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The Archives of Internal Medicine

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THE RENAL FUNCTION IN GOUT*

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BOSTON

That gouty subjects are prone to nephritis has long been recognized. Nevertheless, patients coming to necropsy and in whom uratic deposits are found in the toe joints may show signs of nephritis so meager as to be ascertainable only by microscopic examination of the kidneys.[1] Frequently clinical examination of gouty patients fails to elicit symptoms which permit the diagnosis of chronic nephritis. Because of this the great majority of observers have interpreted the findings of metabolism experiments in gout on the supposition that the functional condition of the kidneys was normal. Since their results were obtained by the study of substances excreted into the urine the importance of knowing the degree of renal function is apparent. Only within a comparatively few years have methods been developed which give trustworthy information concerning efficiency of the kidneys. Using these methods, I have made a study of renal function in gouty patients with tophi. In these the diagnosis of chronic nephritis was either not made or its presence was questionable. The cases are comparable to those reported in the literature on which previous observers have carried out the metabolism studies.

The maximum normal limit of the amount of nonprotein nitrogen in the blood is considered at 35 mg. per 100 c.c., and for urea nitrogen 20 mg. per 100 c.c.[2] The minimum normal of the McLean index[3] of urea excretion is 80 per cent. The normal excretion of phenolsulphonephthalein in two hours ranges between 60 per cent. and 80 per cent. In the two hour renal test[4] specimens of urine were collected every two hours from 7 a. m. to 9 p. m., and one night specimen from

* Submitted for publication May 15, 1917.

* From the Medical Clinic of the Peter Bent Brigham Hospital.

1. Garrod, A. E.: The Chemical Pathology of Gout, Brit. Med. Jour., 1904, **2**, 741.

2. McLean, F. C., and Selling, L.: Urea and Total Nonprotein Nitrogen in Normal Human Blood. Relation of Their Concentration to Rate of Elimination. Jour. Biol. Chem., 1914, **19**, 31.

3. McLean, F. C.: The Numerical Laws Governing the Rate of Excretion of Urea and Chlorids in Man, Jour. Exper. Med., 1915, **22**, 212.

4. O'Hare, J. P.: A Study of Salt, Nitrogen and Water Excretion in Nephritis, The Archives Int. Med., 1916, **17**, 711.

9 p. m. to 7 a. m. In each specimen the volume, specific gravity, total nitrogen, percentage concentration of nitrogen, total salt and the percentage concentration of salt were determined. In the urine of persons with normal kidneys there is considerable variation in each of the above named elements in the different two-hourly specimens. Renal functional changes are indicated by a fixation and lowering of one or several of the elements measured. More than 400 c.c. of urine voided between the hours of 9 p. m. and 7 a. m. is considered an abnormal increase in the night amount. The findings in the two-hour renal test have been interpreted by Dr. James P. O'Hare. To these standard tests one has been added in which the effect of ingesting sweetbreads on the nonprotein nitrogen of the blood is determined. This will be discussed later. For purposes of comparison the first two protocols represent the findings in two patients without gout. In the first case the effect of the ingestion of sweetbreads on the nonprotein nitrogen of the blood and on the excretion of uric acid is given. Detailed studies of the exogenous uric acid excretion in the four succeeding cases have been made and will be reported by Pratt and myself.

TECHNIC

Uric acid in the blood was determined by the methods outlined by Folin.[5] On the advice of Folin the "uric acid reagent" was used instead of the "uric acid-phenol reagent" in quantitating uric acid in the urine. Urea was determined by the urease method of Van Slyke and Cullen.[6] The total nonprotein nitrogen of the blood was estimated by the direct Nesslerization method of Folin and Denis.[7] Nitrogen of the urine was determined by the Kjeldahl method. Chlorids were quantitated by Goodall's modification of Volhard's method.[8]

The results of the renal function studies are given in the following protocols.

PROTOCOLS

Case 1.—R. L. Medical No. 5523. White, man, aged 35.

Diagnosis: Cirrhosis of the liver.

The patient drank large quantities of alcoholic beverages. He had undergone abdominal paracentesis for the removal of ascitic fluid twice in the previous year. His condition at the time of the metabolism experiment was good. Physical examination was essentially negative. There were no evidences of cardiovascular disease. Blood pressure was 130 mm. systolic and 70 mm. diastolic. The liver edge was palpable 3 cm. below the right costal margin.

Clinical pathologic findings in the urine: Nov. 12, 21, and Dec. 12, 1916. Urine amber, clear, acid, specific gravity 1.012 and 1.019, no trace of albumin with the heat and acetic acid test; a rare hyaline or granular cast; no erythrocytes, no pus cells, no epithelium.

---

5. Folin, O.: Laboratory Manual of Biological Chemistry, New York, 1916.

6. Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of Urease and Its Use in the Determination of Urea, Jour. Biol. Chem., 1914, **19**, 211.

7. Folin, O., and Denis, W.: Nitrogen Determination by Direct Nesslerization. Nonprotein Nitrogen in the Blood. Jour. Biol. Chem., 1916, **26**, 491.

8. Goodall, H. W.: An Accurate Rapid Method for the Determination of Chlorid in the Urine. A Critical Study of Short Methodism Vogue. Boston Med. and Surg. Jour., 1909, **160**, 304.

Dec. 2 and 23, 1916. Urine clear, amber, acid; specific gravity 1.015 and 1.022; slightest possible trace of albumin with the heat and acetic acid test; a rare hyaline or granular cast; no pus cells, no erythrocytes, no epithelium.

Oct. 31 and Nov. 2, 1916. Urine clear, amber, acid; specific gravity 1.015; no albumin, no casts, no erythrocytes, no pus cells, no epithelium.

Phthalein excretion: Dec. 1, 1916, 72 per cent. in two hours. The percentage of purin nitrogen in sweetbreads fed which was excreted as uric acid nitrogen was 13.

Date	Time of Collection	Urine		Blood		Remarks
		Amount in C.c.	Uric Acid in Gm.	Nonprotein N in Mg. per 100 C.c.	Uric Acid in Mg. per 100 C.c.	
1916 Dec. 14	.....	.....	....	....	....	Purin-free diet begun
14	.....	.....	....	44.4	1.7	
15-16	7 a. m. - 7 a. m.	1,110	0.53			
16-17	.....	760	0.48			
17-18	.....	435	0.27			
18-19	.....	790	0.41			
19-20	.....	670	0.35			
20-21	.....	595	0.33			
21-22	.....	675	0.37			
22	7 a. m. - 1 p. m.	130	0.06			
	12 N.	.....	....	40.0		
	1 p. m.	.....	....	....	....	150 gm. sweetbreads
	7 p. m.	.....	....	45.6	1.9	
22-23	.....	950	0.62			
23	12 N.	.....	....	41.3	1.4	
23-24	.....	505	0.28			
24-25	1 p. m. - 1 p. m.	620	0.38			

Endogenous output of uric acid December 18-22 = 1.73 gm.

Endogenous output of uric acid per day = 0.35 gm.

Exogenous output of uric acid December 23 = 0.28 gm.

Percentage of purin nitrogen in 150 gm. of sweetbreads according to Burian and Schur = 0.68 gm.

Per cent. of purin nitrogen excreted as uric acid nitrogen = 13.

Effect of a Meal of Sweetbreads on the Uric Acid and Nonprotein Nitrogen in the Blood

Date	Mg. Uric Acid per 100 C.c. Blood	Mg. Nonprotein N per 100 C.c. Blood	Diet of Patient	Remarks
1916 Dec. 14	1.7	44.4	Mixed	Purin-free diet begun
22	...	40.0	Purin-free	
	1.9	45.6	Purin-free	7 hours after a 150 gm. sweetbread meal
23	1.4	41.3	Purin-free	

Summary: The blood uric acid is normal. There is a moderate retention of nonprotein nitrogen with the patient on a mixed diet. No noteworthy retention of nonprotein nitrogen is present after the sweetbread meal.

Summary of Case 1.—Two of three urine specimens examined contained a scant trace of albumin and a rare cast. The significance of these findings will be discussed with those of the following cases. Phthalein excretion was normal. The amount of uric acid eliminated was small. There was a slight but definite increase of total nonprotein nitrogen in the blood when the patient was on a mixed diet. This function can be elicited other than that manifested by the diminution may explain the low output of exogenous uric acid. There was no noteworthy retention of nonprotein nitrogen in the blood after the meal of 150 gm. of sweetbreads, in spite of the fact that retention had occurred when the patient was on a mixed diet.

Case 2.—W. H. K., Medical No. 5278. Woman, white, aged 29.

Diagnosis: Chronic arthritis.

The patient's habits were good. She had had chronic polyarthritis with occasional fairly acute exacerbations for the previous two years. The joints never had been either severely painful or tender. During the previous six months stiffness of the knees had prevented walking. Physical examination was negative except for the joints. There was limitation of motion and crepitation in all joints of the extremities. The elbows, wrists, finger joints, knees, and joints of both halluxes were enlarged, principally as the result of thickening of the periarticular tissues. Blood pressure was 110 mm. systolic and 75 mm. diastolic. Urine examinations were negative except for a scant trace of albumin and a rare cast in one of the specimens. Phthalein excretion was 65 per cent. in two hours.

Two-Hour Renal Test, Nov. 5, 1916

Time	Volume of Urine in C.c.	Specific Gravity	Nitrogen		Chlorids	
			Per Cent.	Gm.	Per Cent.	Gm.
7 a.m. - 9 a.m.	61	1.015	0.67	0.41	0.54	0.33
9 a.m. -11 a.m	72	1.015	0.80	0.64	0.33	0.24
11 a.m. - 1 p.m.	75	1.015	0.77	0.58	0.33	0.25
1 p.m. - 3 p.m.	238	1.010	0.36	0.84	0.18	0.42
3 p.m. - 5 p.m.	237	1.008	0.30	0.71	0.14	0.33
5 p.m. - 7 p.m.	80	1.014	0.68	0.50	0.20	0.16
7 p.m. - 7 a.m.	605	1.012	0.50	3.03	0.28	1.69

Summary of two-hour renal test: Water: no fixation of amount. Increased amount of night urine. Slight fixation of specific gravity. Nitrogen, no fixation. Sodium chlorids, no fixation.

Clinical pathologic findings in the urine: Sept. 13 and 14, 1916. Urine straw colored, slightly turbid, acid; specific gravity 1.012; slightest possible trace of albumin with the heat and acetic acid test; a rare hyaline cast, a few pus and squamous epithelial cells, no erythrocytes. October 3, 12, 22, 25, 26, 27, November 8, 9, 20, and December 2 and 17. Urine straw colored; slightly turbid; acid; specific gravity 1.004 to 1.008. No albumin, no casts, a few pus cells, numerous squamous epithelial cells, no erythrocytes.

Phthalein excretion: Dec. 1, 1916, 65 per cent. in two hours.

McLean index of urea excretion: Nov. 28, 1916, 95.2 per cent.

Percentage excretion of intravenously injected uric acid: Nov. 9 and 12, 1916, 40 per cent.

Percentage of purin base nitrogen of sweetbreads ingested excreted as uric acid nitrogen: Nov. 22 to 24, 1916, 30 per cent.

UREA N, NONPROTEIN AND URIC ACID OF THE BLOOD

Date	Mg. Uric Acid per 100 C.c. Blood	Mg. Nonprotein N per 100 C.c. Blood	Mg. Urea N per 100 C.c. Blood	Diet of Patient
1916 Oct. 31	1.8	....	....	Mixed
Nov. 8	1.6	....	....	Purin-free
9	1.5	27.9	....	Purin-free
22	1.5	....	....	Purin-free
27	...	....	16.3	Mixed

Summary: The uric acid, nonprotein and urea nitrogen are not increased.

CASE 3.—J. G., Medical No. 5421. White, man, aged 43.

Diagnosis: Gout; arteriosclerosis; hypertension; chronic myocarditis; very questionable chronic nephritis.

The patient had used beer freely. He had about sixteen attacks of severe polyarthritis of gouty character during the previous twenty-six years. Physical examination showed numerous tophi in the ears and on the fingers. The joints showed no changes of chronic arthritis. The radial artery walls were sclerosed. The blood pressure was 185 mm. systolic and 117 mm. diastolic. Otherwise physical examination was negative. The urine examination was negative. Phthalein excretion was 53 per cent. in two hours.

Clinical pathologic findings in the urine: Oct. 11, 12, 13, and Nov. 13, 1916. Urine clear, amber, acid; specific gravity 1.014; no albumin with the heat and acetic acid test; no pathologic formed elements.

TWO-HOUR RENAL TEST, NOV. 28, 1916

Time	Volume of Urine in C.c.	Specific Gravity	Nitrogen		Chlorids	
			Per Cent.	Gm.	Per Cent.	Gm.
7 a.m. - 9 a.m.	133	1.020	0.39	0.51	0.78	1.04
9 a.m. -11 a.m.	140	1.015	0.37	0.50	0.66	0.92
11 a.m. - 1 p.m.	158	1.017	0.40	0.63	0.83	1.31
1 p.m. - 3 p.m.	105	1.022	0.37	0.39	0.84	0.88
3 p.m. - 5 p.m.	150	1.006	0.47	0.70	0.97	1.46
5 p.m. - 7 p.m.	260	1.014	0.41	1.07	0.98	2.55
7 p.m. - 9 p.m.	45	1.018	0.52	0.23	0.91	0.41
9 p.m. - 7 a.m.	209	1.016	0.45	1.76	0.96	3.74

Summary of the two-hour renal test: Water: no fixation of volume; slight relative increase in the night amount; no fixation of specific gravity. Nitrogen: slight tendency toward fixation toward afternoon fixation of percentage concentration; no fixation of amount.

March 23 and 28, 1917. Urine clear, amber, acid; specific gravity 1.013; slightest possible trace of albumin, a small number of leukocytes, no epithelial cells, no erythrocytes, no casts.

March 25, 1917. Urine clear, amber; specific gravity 1.009; slightest possible trace of albumin; a rare cast; no erythrocytes, no leukocytes, no epithelial cells.

Phthalein excretion: Oct. 11, 1916, 43 per cent. in two hours; Nov. 6, 1916, 52 per cent. in two hours; March 28, 1917, 42 per cent. in two hours.

McLean index of urea excretion: Nov. 6, 1916, 41 per cent.; March 31, 1917, 1.6 per cent.; April 10, 1917, 2.4 per cent.

UREA N, NONPROTEIN N, AND URIC ACID OF THE BLOOD IN THIS PATIENT WITH GOUT

Date	Mg. Uric Acid per 100 C.c. Blood	Mg. Nonprotein N per 100 C.c. Blood	Mg. Urea N per 100 C.c. Blood	Diet of Patient	Remarks
1916 Oct. 10	6.4	....	....	Mixed	Three days prior to an acute attack of gout
17	5.4	....	....	Purin-free	Acute gout attack
30	4.1	....	....	Purin-free	
Dec. 6	4.0	38.4	11.2	Mixed	
7	4.3	39.0	11.9	Mixed	
1917 March 31	...	....	13	Purin-free	
April 2	...	33.0	....	Purin-free	
4	...	....	....	Purin-free	12 noon, 150 gm. sweetbread eaten
		38.7	....	.....	7 p. m.,
5	...	37.3	14.4	Purin-free	11 a. m., 12 noon, 150 gm. sweetbread eaten
6	...	39.8	....	Purin-free	11 a. m.,
7	..	....	....	.....	12 noon, 150 gm. sweetbread eaten
8	...	....	10.1	.....	12 noon, 150 gm. sweetbread eaten
9	...	37.5			

Summary: The blood uric acid is high. The urea nitrogen is not increased. The nonprotein nitrogen shows a slight increase after the feeding of sweetbreads.

Summary of Case 3.—The evidences of depressed renal function in this case are the low index of urea excretion and the increase in the amount of night urine. The other findings by the two-hour renal test, the slightly lowered phthalein excretion and the slight increase in nonprotein nitrogen are only suggestive of a disturbance in renal function. No abnormal retention of nonprotein nitrogen in the blood occurred after feeding sweetbreads for five days. It is theoretically possible that there is a type of pathologic kidney in which no disturbance in function can be elicited other than that manifested by the diminution in the excretion of uric acid. This case approaches that type more nearly than any of the others studied. The findings in this case do not show indisputable evidence of depressed renal function, but they are strongly indicative of such a condition.

CASE 4.—W. P. G., Medical No. 5471. Negro, man, aged 43.

Diagnosis: Gout; very questionable chronic nephritis.

The patient's habits were good. During the previous ten years he had had a dozen attacks of gout affecting the joints of the lower extremities and of the phalanges of the fingers. On physical examination numerous tophi were found in the ears and about the finger joints. Otherwise, physical examination was negative. The blood pressure was 135 mm. systolic and 95 diastolic. The urine contained no casts, no blood and no epithelium. A scant trace of albumin was found once in the examination of several urine specimens. Phthalein excretion was 42 per cent. in two hours.

Clinical pathologic findings in the urine: Oct. 20, 1916. Urine clear, amber, acid; specific gravity 1.010; the slightest possible trace of albumin with the heat and acetic acid test; no pathologic formed elements. Oct. 21, Nov. 1 and 12, 1916. Urine clear, amber; specific gravity 1.012; no pathologic findings.

Phthalein excretion: Nov. 10, 1916, 42 per cent. in two hours.

McLean index of urea excretion: Nov. 9, 1916, 15.5 per cent.

Percentage excretion of intravenously injected uric acid: Oct. 29, 1916, 14 per cent.

TWO-HOUR RENAL TEST, NOV. 9, 1916

Time	Volume of Urine in C.c.	Specific Gravity	Nitrogen		Chlorids	
			Per Cent.	Gm.	Per Cent.	Gm.
7 a.m. - 9 a.m.	110	1.014	0.62	0.68	0.55	0.61
9 a.m. -11 a.m.	74	1.016	0.77	0.57	4.28	1.21
11 a.m. - 1 p.m.	67	1.015	0.75	0.51	0.22	0.15
1 p.m. - 3 p.m.	72	1.014	0.76	0.55	0.38	0.27
3 p.m. - 5 p.m.	72	1.016	0.74	0.53	0.35	0.25
5 p.m. - 7 p.m.	47	1.016	0.74	0.35	0.22	0.10
7 p.m. - 9 p.m.	96	1.016	0.77	0.73	0.39	0.20
9 p.m. - 7 a.m.	440	1.014	0.72	3.17	0.35	1.54

Summary of two-hour renal test: Water: specific gravity fixed; amount not fixed; relative increase in the amount of night urine. Nitrogen: considerable fixation of the percentage concentration and of the amount. Sodium chlorid: some fixation of the percentage concentration and of the amount.

UREA N, NONPROTEIN N, AND URIC ACID OF THE BLOOD IN GOUT

Date	Mg. Uric Acid per 100 C.c. Blood	Mg. Nonprotein N per 100 C.c. Blood	Mg. Urea N per 100 C.c. Blood	Diet of Patient
1916 Oct. 23	3.3	43.5	....	Purin-free
27	4.1	....	....	Purin-free
28	4.3	....	....	Purin-free
Nov. 29	4.3	49.5	30.3	Mixed

Summary: The blood uric acid is high. There is a definite retention of urea and of nonprotein nitrogen.

Summary of Case 4.—There was the slightest trace of albumin in one of four urines examined. The renal function studies showed a small diminution in the phthalein output, a very low index of urea excretion, a moderate but definite retention of both urea and non-protein nitrogen in the blood and a fixation of specific gravity, a relative increase in the amount of night urine and a fixation of the nitrogen output in the two-hour test. These findings are definite evidences of a considerable disturbance in the function of the kidneys.

CASE 5.—A. L. E., Medical No. 5297. White, man, aged 48.

Diagnosis: Gout; cirrhosis of the liver; questionable nephritis.

The patient had used large quantities of beer and whisky for many years. In the previous five years the patient had had five attacks resembling more the exacerbations of a chronic arthritis than gout. Three of these attacks occurred in the Peter Bent Brigham Hospital. Physical examination showed several tophi in the ears. Blood pressure was 156 mm. systolic and 96 mm. diastolic. The liver edge was palpable 4 cm. below the right costal margin. Otherwise the physical examination was negative. The urine showed occasionally a scant trace of albumin and a few casts. Phthalein excretion was 24 per cent. in two hours.

Clinical pathologic findings in the urine: Five urine examinations were made between Sept. 14 and Oct. 1, 1916. The specific gravity varied between 1.007 and 1.020. Three specimens contained the slightest possible trace of albumin with the heat and acetic acid test, and the other two, none. An occasional hyaline or granular cast, but no other pathologic elements as found in the specimens of urine. Six subsequent urine examinations were made between Oct. 1 and Nov. 24, 1916. No albumin, no casts, no erythrocytes, no pus, and no epithelium were found.

Phthalein excretion: Sept. 18, 1916, 24 per cent. in two hours.

McLean index of urea excretion: Sept. 18, 1916, 25 per cent.; Nov. 14, 1916, 15 per cent.

Percentage of purin nitrogen administered which was excreted as uric acid nitrogen: Nov. 26 and 27, 1916, 5.1 per cent.

TWO-HOUR RENAL TEST, NOV. 14, 1916

Time	Volume of Urine in C.c.	Specific Gravity	Nitrogen		Chlorids	
			Per Cent.	Gm.	Per Cent.	Gm.
7 a.m. - 9 a.m.	19	1.030	0.98	0.19	0.40	0.08
9 a.m. -11 a.m.	70	1.014	0.71	0.50	0.32	0.22
11 a.m. - 1 p.m.	33	1.024	1.19	0.39	0.44	0.15
1 p.m. - 3 p.m.	38	1.022	1.17	0.45	0.36	0.15
3 p.m. - 5 p.m.	16	1.024	1..22	021	0.44	0.07
5 p.m. - 7 p.m.	40	1.022	1.02	0.41	0.26	0.10
7 p.m. - 9 p.m.	40	1.018	0.92	0.37	0.24	0.10
9 p.m. - 7 a.m.	235	1.018	1.01	2.37	0.43	1.11

Summary of the two-hour renal test: Water: no fixation of amount but the output was small. No fixation of specific gravity. Output of night urine relatively increased. Nitrogen: no fixation. Sodium chlorid: no fixation.

UREA N, NONPROTEIN N, AND URIC ACID OF BLOOD IN GOUT

Date	Mg. Uric Acid per 100 C.c. Blood	Mg. Nonprotein N per 100 C.c. Blood	Mg. Urea N per 100 C.c. Blood	Diet of Patient	Remarks
1916 Oct. 15	4.6	....	....	Purin-free	Acute attack of gout
Nov. 3	3.5	52.6	....	Purin-free	
14	...	....	27.5	Purin-free	
25	4.5	54.3	....	Purin-free	
	5.3	74.3	....	Purin-free	Seven hours after a meal of 150 gm. sweetbreads
26	4.8	73.0	....	Purin-free	
Dec. 4	5.3	66.6	....	Mixed	

Summary: The blood uric acid and urea nitrogen are high. There is a retention of nonprotein nitrogen especially marked after the sweetbread meal.

Summary of Case 5.—The occasionally slight trace of albumin and rare casts found in the urine in this case were present during or near the time the patient was suffering with a gouty attack. Definite evidences of depression of renal function are the low phthalein excretion, the decrease in the index of urea excretion, a relative increase in the amount of night urine in the two-hour test, the increase in urea and nonprotein nitrogen in the blood, and the retention of nonprotein nitrogen after feeding 150 mg. of sweetbreads. These findings show very conclusively that there was a marked disturbance in the functional capacity of the kidney. But whether or not these findings justify the diagnosis of chronic nephritis is at present not known.

CASE 6.—J. F. S., white, man, aged 42.

Diagnosis: Gout.

The patient was a heavy beer drinker. He had had numerous attacks of monoarticular and of polyarticular arthritis of typical gouty character in the previous ten years. Physical examination was negative except for tophi in the ears, about the knuckle joints of the left hand and just above the olecranon processes of both ulnae. There were no evidences of cardiovascular disease. Blood pressure was 144 mm. systolic and 90 mm. diastolic.

Clinical pathologic findings in the urine: Feb. 4, 1917. Urine: amount, 2,200 c.c.; clear, amber, acid; specific gravity 1.020; no albumin with the heat and acetic acid test; an occasional hyaline cast; a few pus cells; no epithelium, no erythrocytes. Feb. 17, 1917. Urine clear, yellow, acid; specific gravity 1.017; slightest possible trace of albumin with the heat and acetic acid test; no casts, no epithelium, no erythrocytes; a moderate number of pus cells. Feb. 18, 1917. Urine clear, yellow, acid; specific gravity 1.018; slightest possible trace of albumin with the heat and acetic acid test; no erythrocytes; a moderate number of pus cells; no epithelium.

Phthalein excretion: Jan. 30, 1917, 15 per cent. in two hours; Feb. 9, 1917, 38 per cent. in two hours.

McLean index of urea excretion: Feb. 5, 1917, 29.5 per cent.; Feb. 18, 1917, 22.5 per cent.

TWO-HOUR RENAL TEST, FEB. 11, 1917

Time	Water, C.c.	Specific Gravity	Nitrogen		Salt	
			Per Cent.	Gm.	Per Cent.	Gm.
7 a.m. - 9 a.m.	174	1.017	0.31	0.54	0.87	1.69
9 a.m. -11 a.m.	87	1.017	0.36	0.31	0.68	0.59
11 a.m. - 1 p.m.	99	1.019	0.42	0.41	0.69	0.69
1 p.m. - 3 p.m.	231	1.019	0.28	0.64	0.83	1.91
3 p.m. - 5 p.m.	232	1.017	0.34	0.07	0.81	1.88
5 p.m. - 7 p.m.	241	1.019	0.40	0.97	0.90	2.17
7 p.m. - 9 p.m.	233	1.019	0.55	1.31	0.74	1.72
9 p.m. - 7 a.m.	423	1.017	0.53	0.22	0.78	3.30

Summary of two-hour renal test: Water: fixation of specific gravity at a high level; afternoon fixation of amount; night amount relatively increased. Nitrogen: no fixation. Sodium chlorid: slight fixation of percentage concentration; no fixation of amount.

URIC ACID, UREA AND NONPROTEIN NITROGEN OF THE BLOOD IN GOUT

Date	Mg. Uric Acid per 100 C.c. Blood	Mg. Nonprotein N per 100 C.c. Blood	Mg. Urea N per 100 C.c. Blood	Diet of Patient	Remarks
1917 Jan. 30	5.8	47.6	....	Mixed	
Feb. 5	...	44.6	25.2	Purin-free	
22	...	....	27.4	Purin-free	11 a.m. and 11:15 a.m., patient given 150 gm. sweetbreads
		43.5	28.9	Purin-free	6 p. m., same
23	...	48.8	36.6	Purin-free	11 a. m., same

Summary: The uric acid and nonprotein nitrogen are increased with the patient on a mixed diet. A retention of nonprotein nitrogen follows the sweetbread meal.

Summary of Case 6.—A few casts were found in the urine on two of four examinations. The scant trace of albumin occasionally present may be accounted for by the pus cells which were found. The diagnosis of nephritis was not made in this patient. The evidences of depression in renal function are the low phthalein output, the low index of urea excretion, the retention of nonprotein nitrogen in the blood on a mixed diet and the retention of both nonprotein and urea nitrogen after the sweetbread meal.

CASE 7.—F. J. S., Medical No. 6151. White, man, aged 43.

Diagnosis: Gout; obesity.

The patient's habits were good. During the past ten years he had had numerous attacks of arthritis either in one or both of the lower extremities. Physical examination was essentially negative. There were no signs of cardiovascular

disease. Blood pressure was 130 mm. systolic and 90 mm. diastolic. A tophus was present in the right ear and from it sodium urate crystals were obtained.

Clinical pathologic examination of the urine: Feb. 19, 1917. Urine clear, amber, acid; specific gravity 1.022, slightest possible trace of albumin with the heat and acetic acid test; no pathologic formed elements. Feb. 25, 1917. Urine examination negative. March 3, 1917. Urine clear, amber, acid; specific gravity 1.011; no albumin, no sugar; one hyaline cast found; no other formed elements present.

Phthalein excretion: Feb. 17, 1917, 50 per cent. in two hours; March 1, 1917, 21 per cent. in two hours.

McLean index of urea excretion: Feb. 17, 1917, 44.2 per cent.; Feb. 27, 1917, 16.2 per cent.; March 1, 1917, 35.7 per cent.

TWO-HOUR RENAL TEST, FEB. 22, 1917

Time	Water, C.c.	Specific Gravity	Nitrogen		Salt	
			Per Cent.	Gm.	Per Cent.	Gm.
7 a.m. - 9 a.m.	88	1.027	1.26	1.11	0.50	0.44
9 a.m. -11 a.m.	96	1.025	1.62	1.56	0.49	0.42
11 a.m. - 1 p.m.	107	1.025	1.21	1.30	0.57	0.61
1 p.m. - 3 p.m.	99	1.024	1.22	1.21	0.33	0.33
3 p.m. - 5 p.m.	100	1.023	1.33	1.44	0.41	0.45
5 p.m. - 7 p.m.	158	1.019	0.79	1.26	0.46	0.73
7 p.m. - 9 p.m.	142	1.020	0.87	1.28	0.52	0.74
9 p.m. - 7 a.m.	511	1.009	1.03	5.26	0.46	0.24

Summary of two-hour renal test: Water: no fixation of amount; tendency toward fixation of specific gravity but ability to concentrate retained; night amount increased. Nitrogen: no fixation. Sodium chlorid: no fixation.

Date	Mg. Uric Acid per 100 C.c. Blood	Mg. Nonprotein N per 100 C.c. Blood	Mg. Urea N per 100 C.c. Blood	Diet of Patient	Remarks
1917 Feb. 17	...	....	24.7	Mixed	Very little meat in diet
23	4.9	48.6	25.8	Purin-free	10 a. m.; 11 a. m., patient received 150 gm. sweetbreads
		57.9	32.4	Purin-free	6 p. m.
24	...	50.0	28.8	Purin-free	11 a. m.
27	...	55.5	28.3	Purin-free	

Summary: The blood uric acid is increased. There is a retention of nonprotein nitrogen and to a less extent of urea nitrogen, both being considerably increased for several days after the sweetbread meal.

Summary of Case 7.—The scant trace of albumin and the one cast found in the urine were present at a time when the patient was febrile during an attack of gout. There were no signs of chronic nephritis in this patient. The evidences of depressed renal function are the low

phthalein output and the low index of urea excretion, the increased amount of night urine in the two-hour test, and the retention of urea and nonprotein nitrogen in the blood after the sweetbread meal. These findings show a definite derangement in the function of the kidneys.

SUMMARY OF THE RENAL FUNCTION IN GOUT

We have studied the renal function in two nongouty and in five gouty patients with tophi. The more important findings obtained in the gouty persons are given in the accompanying table.

TABLE GIVING SYNOPSIS OF THE FINDINGS BY THE RENAL FUNCTION TEST IN GOUT

Case	Phthalein Excretion, per Cent.	McLean Index, per Cent.	Mg. Nonprotein N per 100 C.c. of Blood	Mg. Urea N per 100 C.c. of Blood	Mg. Nonprotein N per 100 C.c. Blood after Sweetbreads	Excretion of Exogenous Uric Acid in per Cent.	Positive Findings in Two-hour Renal Test
3	43 52 42	41.0 1.6 2.4	39.0	11.9	37.3	0	Increased amount of night urine
4	42	15.5	49.5	30.3	....	14	Fixation of specific gravity, of amount and percentage concentration of N
5	24	25	54.3	27.5	74.3	0	Relative increase of night urine
6	15	29.5	47.6	....	....	..	Fixation of specific gravity
	38	22.5	44.6	25.3	48.8	..	Night amount relatively increased
7	50 21	44.2 16.2 85.7	....	28.6	50.0	..	Increased amount of night urine

The table shows that a considerable variation existed in the findings obtained by the tests for renal function both among the different cases and in the same case. Nevertheless, the results obtained by a series of any one test were consistent in the same case. There was considerable increase in both the nonprotein and urea nitrogens in the blood in all but one case. The McLean index of urea excretion was much below the normal in all cases. The two-hour renal test gave definite evidences of disturbed renal function in four cases and suggestive evidence in one.

A scant trace of albumin was present in one urine of Case 4. In the remaining five cases of gout scant traces of albumin and a few casts were present in certain of the urine specimens. It will be noted that similar findings were obtained in two nongouty, nonnephritic cases (1 and 2). The occasional finding of scant traces of albumin and a

small number of casts in the urine is not considered as indicative of chronic nephritis. Such urinary findings, although evidence of temporary renal damage, are too commonly present in pathologic conditions not connected with kidney lesions to be interpreted as the result of a chronic nephritis. The question of the existence of that disease in our cases of gout was raised by the abnormal findings in the studies of renal function.

To the list of renal function tests has been added the study of the total nonprotein nitrogen in the blood after a meal of 150 gm. of sweetbreads. The amounts fed were not unduly large and should cause no rise in the nonprotein nitrogen in the blood in a person with normal kidneys. No retention of this nitrogen occurred in the patient with alcoholic cirrhosis (Case 4) in spite of the fact that a slight increase was present on a mixed diet. Likewise no retention of nonprotein nitrogen in the blood was found after a meal of 150 gm. of sweetbreads in a case of acute infectious arthritis and congenital heart disease, and also in gout (Case 3). The patient with arthritis was chosen because of the constant presence of a scant trace of albumin and casts in the urine. The amounts of nonprotein nitrogen in the blood in this case were 37.5 mg. before the sweetbread meal and 40 mg. twenty-four hours afterward.

In all the cases of gout there was definite depression of renal function as measured by some of the tests. It is, therefore, fair to assume that the diminution in or the absence of excretion of exogenous uric acid and of other nitrogenous substances in these cases of gout may be due to renal retention and not to the result of derangements in the intermediary metabolism of the nucleins. These cases, however, do not exclude the possibility that the decreased renal function is secondary to the gout and that the uric acid retention was present before there were signs of retention of other nitrogenous substances. It is important to know whether disturbances in renal function occur in the first stages of gout. We have not had early cases for study. In such cases there would be the uncertainty of knowing whether they were really gout or not, since the only pathognomonic sign is the deposition of sodium urate crystals, and this is a late manifestation.

SUMMARY AND DISCUSSION

The apparently frequent occurrence of decreased renal function in cases of typical gout justifies a word of caution against assuming that the faulty excretion of uric acid and of other nitrogenous substances when found is due to derangements in metabolism. It may be due to renal retention as was suggested by Garrod[9] in 1848. Whichever

9. Garrod, A. B.: Observations on Certain Pathological Conditions of the Blood and Urine in Gout, Rheumatism and Bright's Disease, Med.-Chirurg. Trans., 1848, **31**, 83.

happens, uric acid may still be the cause of the symptoms or at least closely related to them. The theories of Umber,[10] Brugsch and Schittenhelm,[11] Minkowski[12] and others regarding the rôle of the nuclein metabolism and of uric acid in the etiology of gout grow untenable in proportion to the evidence of a deranged renal excretion in gouty persons. Umber advanced the hypothesis that the failure of gouty persons to excrete exogenous uric acid was due to a special affinity of the tissues for uric acid. On the other hand, Minkowski offered the explanation that the uric acid entered into chemical combinations in the blood which prevented its excretion by the kidneys. Chemical methods are not available for the proof or disproof of the theories of either of these two authors. But the finding of deficiency in the renal function of gout offers a simpler explanation for the phenomenon. A. E. Garrod[1] says: "If the fault is in the kidneys alone, gout must be removed once and for all from the category of metabolic disorders and placed among the sequelae of renal inadequacy, at least in so far as the uric acid phenomena of the disease are concerned."

Kionka[13] revived the theory that gout was the result of functional disturbances of the liver. This was based on the finding that glycocoll accelerated the precipitation of a monourate from a solution of biurate, and on the observation that glycocoll had been found in the urine of gouty persons. Frey[14] attempted to prove Kionka's theory by certain experimental work, but Abderhalden and Schittenhelm[15] have shown that his results were erroneous. Hirschstein[16] reported that glycocoll was present in the urine of gouty patients in much greater quantities than in health. On the basis of Hirschstein's work, Umber has concluded that there is a disturbance in the intermediary metabolism in gout. Samuely[17] was unable to confirm Hirschstein's findings regarding the derivation of glycocoll from uric acid. The method used by Hirschstein to determine the amount of glycocoll in the urine is not

10. Umber, F.: Ernährung und Stoffwechselkrankheiten. Berlin, 1914.

11. Brugsch, T., and Schittenhelm, A.: Die Nukleinstoffwechsel und seine Störungen.

12. Minkowski, O.: H. Nothnagel's specielle Path. u. Therap., 1903, **7**, 202.

13. Kionka, H.: Glykokoll und Harnstoff in ihren Beziehungen zur Harnsäure. Eine theorie der Gicht. Ztschr. f. exper. Path. u. Therap., 1905-1906, **2**, 17.

14. Frey, E.: Physikalisch-chemisches Verhalten des Glykokolls und Harnstoff bei der Gicht. Ztschr. f. exper. Path. u. Therap., 1905-1906, **2**, 26.

15. Abderhalden, E., and Schittenhelm, A.: Bemerkungen zu den Arbeiten von Frey über die Rolle des Glykokolls bei der Entstehung der Gicht. Ztschr. f. exper. Path. u. Therap., 1905-1906, **2**, 431.

16. Hirschstein, L.: Die Beziehungen des Glykokolls zur Harnsäure. Ztschr. f. exper. Path. u. Therap., 1907, **4**, 118.

17. Samuely, F.: Bemerkung zu der Arbeit von L. Hirschstein: die Beziehungen des Glykokolls zur Harnsäure. Ztschr. f. exper. Path. u. Therap., 1907, **4**, 558.

quantitative,[18] and this renders his findings questionable. Furthermore, the connection between uric acid and glycocoll as advanced in the theory proposed by Umber is questionable, since the human organism does not decompose uric acid. To accept Umber's theory requires the assumption of the development of new and complex factors in intermediary metabolism, for which there is no satisfactory evidence.

Brugsch and Schittenhelm have upheld the view that in gout there is a disturbance in the intermediary metabolism of the nucleins. Their most important experimental findings have been verified by Levene and Kristeller[19] in this country. The considerations which led Brugsch and Schittenhelm to formulate their theory of the etiology of gout are as follows:

1. The endogenous output of uric acid in gout is less than in normal man, but the amount in the blood is greater. They concluded from these findings that there was a retarded uric acid destruction in the gouty person.

2. If purin or nuclein containing materials were added to the purin-free diet of a gouty patient the elimination of exogenous uric acid was lower in quantity and more protracted in time than in health. From these findings they formed the hypothesis that there was a retarded formation and a retarded elimination of uric acid in gout.

The above conclusions drawn by these two investigators concerning the rôle of nucleins in the production of gout become doubtful for the following reasons:

1. It is generally agreed that uric acid cannot be destroyed by the human organism.[20]

2. Pratt and I[21] have shown that a protracted elimination of exogenous uric acid is not peculiar to gout.

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18. Samuely, F.: See Footnote 17. Fischer, E., and Bergell, P.: Ueber die Derivate einiger Dipeptide und ihr Verhalten gegen Pankreas-fermente. Berichte d. deutsch. chem. Gesellsch., 1903, **36,** 2593. Abderhalden, E., and Bergell, P.: Ueber das Auftreten von Monoaminosäuren im Harn von Kaninchen nach Phosphorvergiftung. Ztschr. f. physiol. Chem., 1903, **39,** 464. Brugsch, T., and Schittenhelm, A.: Ueber den Abbau von Glykokoll und Alanin beim gesunden und gichtkranken Menschen. Ztschr. f. exper. Path. u. Therap., 1907, **4,** 538.

19. Levene, P. A., and Kristeller, L.: Nitrogen and Nuclein Metabolism in Gout. Jour. Exper. Med., 1912, **16,** 303.

20. Soetbeer, F., and Ibrahim, J.: Ueber das Schicksal eingeführter Harnsäure im menschlichen Organismus. Ztschr. f. physiol. Chem., 1902, **35,** 1. Wiechowski, W.: Ueber die Zersetzlichkeit der Harnsäure im menschlichen Organismus. Arch. f. exper. Path. u. Pharmakol., 1908-1909, **60,** 185. Wells, H. G.: Some Additions to Our Knowledge of Purin Metabolism and Their Bearing on the Problem of Gout. Internat. Clin., 1916, **26,** 319. Jones, W.: Nuclein Acids, Their Chemical Properties and Physiological Conduct. Monographs on Biochemistry, New York, 1914.

21. To be published.

3. In the investigation here presented it has been shown that the kidney in gouty patients usually is functionally deficient, and this can explain the low output of exogenous uric acid in gout.

Although the considerations advanced in support of the theory of Brugsch and Schittenhelm may have other explanations as noted above, nevertheless their contention with regard to a relation between nuclein metabolism and gout is not disproved.

The purpose of this discussion has been to emphasize the facts that (1) many of the findings which have heretofore been considered due to disturbances of nuclein metabolism in gout may be explained as the result of renal inadequacy, and (2) that the theories concerning the etiology of gout remain hypotheses without satisfactory experimental bases.

The finding of renal deficiency in gouty persons renders the value of the study of exogenous uric acid elimination as an aid in the diagnosis of gout questionable. Before the status of exogenous uric acid excretion as a symptom of gout can be established a study of the output of uric acid in the different types of nephritis must be made.

CONCLUSIONS

1. The gouty kidney is often functionally deficient.

2. The faulty elimination of exogenous uric acid and of other nitrogenous substances by gouty persons may be the result of depression of the functional power of the kidneys.

3. While renal retention explains many of the anomalies occurring in the excretion of uric acid and of other nitrogenous substances in gout, nevertheless this does not explain the nature of gout, nor does it preclude the possibility of there being an underlying perversion of metabolism.

I am indebted to Dr. B. Smith of Los Angeles, and to Drs. J. P. O'Hare and E. Smith for assistance in certain of the renal function tests. I wish to express my thanks to Dr. H. A. Christian for many helpful suggestions. I am indebted to Dr. Otto Folin for advice as to chemical methods. Dr. A. A. Hornor was kind enough to send me one of the cases from the Boston City Hospital.

AMYOTONIA CONGENITA OF OPPENHEIM

A REPORT OF SIX CASES, WITH A FULL REVIEW OF THE LITERATURE *

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INTRODUCTION

In 1900, Oppenheim[1] called attention to a syndrome which has since been designated as "Oppenheim's Disease."

He had repeatedly observed, in the first months of infancy, and during the first and second years of life, a disease with which he was not acquainted and one of which he could find no mention in the literature.

In this disease he observed immobility of the whole body, or of certain parts of the body, especially of the lower extremities; the parts affected were flaccid; the main symptom was the striking flaccidity, hypotonia or atony of the muscles, which was associated with complete loss or with very much diminished tendon reflexes. In most cases only the legs were affected; in one 8-month-old infant the muscles of the back and the neck were also affected; the child could not sit up nor support its head upright. The muscles of the eyes, tongue and deglutition did not become involved; the diaphragm functionated properly; the intercostal muscles on the contrary seemed to be affected.

The muscles felt flaccid and soft; they appeared thin and devoid of fat, but they did not give the impression of the presence of atrophy.

The electrical reactions showed a quantitative diminution up to complete loss of electrical irritability.

The intelligence, the sensations and the cerebral functions were not disturbed; from the symptoms it appeared to him that he was dealing with a congenital syndrome, even though the symptoms did not always manifest themselves at birth.

He believes that in this disease he was not dealing with an affection of the central nervous system, but with a primary muscle disease, which is due to a delayed and arrested development of the musculature; he does not, however, exclude the possibility that the primary seat of the delayed development may be in the anterior horn cells and not in the muscles; this condition is subject to more or less complete

* Submitted for publication April 30, 1917.

1. Oppenheim: On General and Localized Atony of the Muscles (Myotonie) in Young Children. Monatschr. f. Psychiat. u. Neurol., 1900, **8**, 232.

cure, and thus he accounts for the infrequency of this condition in older children.

A review of the literature reveals that many of the statements made by Oppenheim must be modified in the light of our present knowledge, but it is certain that the syndrome to which he called attention is a distinct entity.

Of the 136 cases reported in the literature, thirty were reported by Americans (Spiller, Gastonguay [Canadian], Laffer, Skoog [three cases], Courtney, Strauch, Zohorsky, Beling, Foot, Faber [three cases], Gordon [two cases], Schlivek, Griffith, Haberman [two cases], Reuben [six cases], Councilman, Dunn [two cases]); twenty-six by Italians; thirty-three by Germans; twenty-one by Englishmen (one from Ireland by Purser); seventeen cases by Frenchmen; three by Belgians; two by Dutchmen; one by a Swiss, and one by a Russian.

In studying a new disease it was thought more advisable to include the doubtful cases than to omit them in this general survey; when our knowledge of this disease becomes more profound, it will be possible to weed out a number of cases which have been included, and possibly many cases have been omitted which rightly belong to this disease. Every case of this disease indexed in the Index Medicus was carefully reviewed. Many cases have been included which are reported as belonging to this disease, but the essential details of which were lacking in the reports. A number of cases have been reported several times by different observers; these have been omitted in the tabulations. The first case with necropsy report was reported by Spiller in 1905; since that time, twenty-six necropsies and six biopsies have been recorded.

Various names have been suggested for this new disease: amyotonia congenita (Oppenheim); congenitale muskelatonie (Tobler); maladie d'Oppenheim (Baudouin); congenital hypotonia or amyoplasia (Coombs); myopathy infantile type (Batten); congenital atonic pseudoparalysis (Haberman); and amyotonia congenita of Oppenheim (Collier and Wilson). The last seems the best, and is the one most widely employed; as Oppenheim has described several diseases which are known by his name, it is always best to use the cognomen, amyotonia congenita.

REPORT OF CASES[2]

CASE 1.—*History.*—Julia B., aged 5½ months, was born prematurely at the end of the eighth month; labor was easy and lasted only six hours; the parents were married four years; there was no history of any miscarriages (the patient

2. Case 1 was kindly referred to me by Dr. Horwitt; the other cases were observed in the Pediatric Department of Vanderbilt Clinic, College of Physicians and Surgeons.

was the first born); the parents were not related to each other; there was no history of any muscular or nervous disease in any of the immediate relatives. Fetal movements were never distinctly felt by the mother; the infant weighed 6 pounds at birth, and was exclusively breast fed for four months, at which time the mother put the infant on complementary feeding. The mother felt that as the infant was growing older, the suction power gradually decreased, and at 4 months the infant was no longer able to express more than a few drops of milk from the breasts, although there was considerable milk in them. There was no history of vomiting in the infant and the bowels were markedly constipated.

Physical Examination.—The head looked like an inverted pear; the face was full, immobile, expressionless and statuesque; it was devoid of all lines which give individuality, and it was small in comparison with the size of the head. The neck was short; no neck was seen from the front, on account of the constant position of the chin on the sternum; a double chin was distinctly to be noted; the arms were held in a peculiar position; the arms were abducted, the forearms were flexed at the elbows, and the hands were pronated, so that the thumbs were nearest to the body; the contour of the arms was normal; the muscular volume appeared not to be diminished; the child appeared to be

Fig. 1.—Case 1, girl, J. B.

better nourished than the weight would indicate. The trunk and spine presented nothing abnormal on inspection. The legs and feet appeared normal in contour and in volume, and were symmetrical; they were held in a peculiar position; the thighs were abducted, the knees flexed and the feet everted. The patient could not sit up unsupported, the head fell forward on the chest. Marked postural kyphosis developed. No abnormal involuntary movements were noted (no tremors, twitchings, choreiform movements, athetosis, spasms, tics or convulsions). The tegumentary status was normal except that the sweat secretion was very marked. There were no vasomotor disturbances to be noted, except that the feet were distinctly cyanosed and colder than the rest of the body; the skin over the feet looked mottled (marble like). There was no edema.

Mensuration gave the following dimensions: head, 16 inches; chest, 13¾ inches; abdomen, 14½ inches; length, 22½ inches, and weight, 10 pounds, 10 ounces.

On palpation the skin appeared normal, but it could not be wrinkled apart from the underlying tissues; the panniculus adiposus was everywhere well developed; the consistency of the muscles appeared to be soft, and could

nowhere be felt apart from the subcutaneous fat; one always had the feeling that the skin, the subcutaneous fat and the muscles constituted one inseparable mass of tissue.

The gastro-intestinal tract appeared to be normal, except that the bowels were always markedly constipated; the breathing was almost entirely abdominal; however, weak contractions of the intercostal muscles were noted.

The deep (tendon) reflexes were all abolished; no clonus could be obtained anywhere (ankle, patella, wrist or jaw); the superficial or cutaneous reflexes were also abolished, only the conjunctival and the pharyngeal reflexes were present. There was no Babinski's reflex, no Kernig's sign and no Oppenheim's sign.

Myosthenic Status: The infant could not support head in sitting posture nor could it sit unsupported; in the recumbent position it could not move head in any direction nor could it change the position of its body to the slightest degree; when called it turned its eyes in the direction of the voice; the arms could be moved; the infant could bring its hands to the mouth, but it could not support arms above the horizontal position; when the arms were elevated they fell as if dead; there seemed to be inhibition in the movements of the fingers, the proximal muscles of the arms seem to be much more affected than the distal. The legs could not be moved at all; no matter in what position they were put, they remained in that position indefinitely; only fine movements of the toes were noted; when the child was immersed in luke warm water a certain amount of movement in the feet and legs could be seen; no abnormal associated movements were present; the muscles were everywhere hypotonic; contractures were not present.

Electrical Reactions: There was complete loss of reaction to strong faradic currents, and marked diminution to galvanic stimulation; the infant could (apparently) tolerate very strong currents without any evidence of pain (due to disappearance of end nerve plates?). The sensation to pain seemed to be diminished both to electric stimulation and to needle pricks.

Cranial Nerves: The fundi were examined and were found to be negative. There was no ptosis nor strabismus; nystagmus was not present; the pupils were equal and reacted to light and accommodation; the facial nerve seemed to be involved. There was lack of facial expression, the left side seemed to be more affected, because there was considerably more drooping of the corner of the mouth on that side; the vagus seemed also to be involved. The voice was weak and "gargling like"; when the child cried it cried with its voice but not with its face (like a ventriloquist); a faint appearance of a smile could occasionally be discerned. Swallowing was difficult, and there always seemed to be some mucus at the back of the throat which the infant could neither swallow nor bring up. Suction was difficult and the infant had to be weaned because it could no longer express the milk from the breasts. The movements of the tongue were normal. Mentality was normal; the infant knew its parents.

Serology: The Wassermann reaction of the mother was negative.

Bones and Joints: Mobility (passive) in all the joints was hyperexcessive. Roentgen-ray examination of the wrist showed the development of a normal number of centers of ossification and no pathologic condition of the bones. Roentgen-ray examination of the head showed nothing abnormal; the pituitary was not enlarged.

In the few weeks that the child was under observation, there was slight improvement in the motor powers.

Case 2.—*History.*—In the family to be described, the three children who were born in the four years of married life were all similarly affected, and all died of pneumonia before they were 1 year old. The parents were not related to each other; there were no similar cases in any of the immediate relatives; there was no history of miscarriages; the Wassermann reaction of the mother was negative. The first child, A. L., came to my notice in 1914

at the age of 3 months; the second, Y. L., at the age of 6 months in August, 1915, and the third, S. L., at the age of 10 weeks in October, 1916.

A. L., girl, was the first born. The birth weight about 8 pounds. The child was born at full term. The labor was normal and easy. From birth the mother noted that the infant was not like other children, inasmuch as it did not move its legs, arms or head. The infant did not nurse well although the mother had plenty of milk, and was gradually losing in weight. The bowels were always markedly constipated.

Physical Examination.—The infant could never hold its head up or move it in any direction; there was gradual deterioration in all its motor powers. The nutrition gradually failed on account of the lack of suction and swallowing power; all deep and superficial reflexes were absent; no electrical reactions were taken. There was marked flaccidity of all the muscles and hypermobility (passive) in all the joints. The chest was deformed (marked lateral recessions) and the breathing was entirely abdominal. The infant died of pneumonia at 4 months.

CASE 3.—*History.*—Y. L., girl, was the second child. The labor was normal and easy. The birth weight was 7 pounds. The first teeth appeared at 6 months. At 6 weeks the child weighed 8 pounds, at 6 months, when it was first brought to my notice, it weighed 10 pounds, 8 ounces. Immediately after nursing ten minutes, the weight was the same. Although there seemed to be plenty of breast milk the child was not able to express the milk from the breasts. The bowels were always constipated.

Physical Examination.—The head appeared large and looked like an inverted bell; the face was small, the chin was small, receding, inconspicuous, and was always kept on the sternum. The head was turned to one side owing to contracture of the sterno-cleidomastoid muscle on one side. The neck was short and could not be seen from the front on account of the position of the chin. The arms were mobile from the elbows below. There was drop wrist on the right side. The chest was deformed (lateral depressions and increased anteroposterior diameter with marked depression of the lower portion of the sternum). The legs and the feet were immobile. The position of the legs was peculiar: The thighs were adducted, the knees were flexed and the feet were rotated outward. No abnormal movements were noted except frequent rotatory movements of the right hand (drop wrist), as if always attempting to extend the dropped wrist. The breathing was rapid and entirely abdominal. The mentality appeared normal.

Mensuration gave the following figures: head, 15¼ inches; chest, 13¼ inches; abdomen, 14 inches; length, 24 inches, and weight, 10 pounds, 9 ounces.

On palpation the skin appeared normal. The muscles were very flabby everywhere and were very soft; they could not be distinguished from the skin and the subcutaneous tissue. The general appearance of the child gave one the impression that the infant was well nourished and of considerably greater weight than it really was; this is due to the deceptive appearance brought about by the preservation of the panniculus adiposus.

Reflexes: The deep and superficial reflexes were all abolished, the conjunctival and the pharyngeal reflexes were present. There was no Babinski's reflex, and no Oppenheim's sign.

Myasthenic Status: The infant could not support its head; it would always fall to the left side. The child could not move the head in any direction; when its attention was attracted it would turn its eyes but not its head in that direction. Rising from recumbent position was impossible. There was complete paralysis of the intercostal muscles. No thoracic respiration was observed. The legs were completely immobile. The infant could never change its position; it always remained in whatever position it was put; the only

motions possible were those in the forearms, hands, fingers and toes. The child was able to flex the forearms and could bring the left hand to the mouth. The right hand was continually rotated as if attempting to extend the wrist and to bring the right hand to the mouth; there were no active motions in any other joints; on passive motion all movements were exaggerated in all the joints.

Electrical Reactions: There was marked diminution to faradic and galvanic stimulation. There was no reaction of degeneration.

Sensory Examination: The infant could tolerate very strong currents without evincing pain; the prick of a needle produced much less apparent pain than in normal infants.

Cranial Nerves: All seemed normal, except the muscles innervated by the facial and the vagus. The face was immobile, expressionless. Nursing was difficult, due to the involvement of the muscles of the lips and the face. Swal-

Fig. 2.—Case 3, girl, Y. L.

lowing was difficult. The voice was feeble, guttural and deep. The infant always cried without the face showing any evidence of it. The child frothed at the mouth, due to inability to swallow saliva.

Progress: During the time the infant was under observation, it did not gain in weight on account of the growing difficulty in suction and swallowing; in the last few weeks of life the infant was fed with a Breck feeder. There was distinct improvement in the motor power of the feet. At 8 months the infant developed pneumonia, from which it did not recover.

Roentgen-ray examination of the wrists showed a normal development of ossification centers, and nothing pathologic of the bones; roentgen-ray examination of the head gave a normal result. The pituitary was not enlarged.

Case 4.—S. L., girl, aged 10 weeks. The appearance of this child was strikingly similar to that of its sister, Y. L.; no one could distinguish one from the other. Y. was a duplicate of S. in every detail; the facial expression, the

complete immobility, the whining and feeble voice, the deformity of the chest, the abdominal breathing, the difficulty in swallowing and in suction were absolutely the same in both; S. lacked the contracture and the drop wrist of its sister Y. Weight at 10 weeks was 10 pounds, 9 ounces. Constipation was marked. This infant like the first, died at 4 months of pneumonia. Improvement was never noted.

Case 5.—*History.*—Ethel P., aged 8 months, second child, was born at term. The labor was normal and easy. There was no history of any convulsions. The birth weight was 9 pounds. The first teeth appeared at 8 months. The Wassermann reaction of the mother was negative. The infant was breast fed. Weight at 8 months was 18 pounds, 3 ounces.

General Examination.—Inspection: The face appeared normal. Convergent strabismus was present. The neck was normal. The arms appeared as if too long for the size of the child; there was no voluntary motion of the arms;

Fig. 3.—Case 6, boy, J. B.; Case 5, girl, E. P.

they were held in a peculiar position; they were abducted, flexed at the elbows, and the hands were pronated. The trunk was immobile, the legs and feet were also immobile; there was adduction of the thighs, slight flexion at knees and outward rotation of the feet. There were no abnormal involuntary movements. There was marked lateral depression of the chest with depression of the lower part of the sternum.

Mensuration: The head was 18¾ inches; chest, 18 inches; abdomen, 18 inches, and the length 28½ inches.

Palpation: The muscles everywhere seemed to be soft and flabby (the abdomen was distended and constipation was marked, due to flabbiness of abdominal muscles).

Reflexes: None could be elicited, except the pharyngeal; the conjunctival also could not be elicited. There was no Babinski's reflex and no Oppenheim's sign.

Myasthenic Status: The child could not support its head; it wabbled like a balloon; nor could it sit up unsupported. When it was supported, marked static kyphosis was observed. The infant could not move its head in any direction; the arms were entirely immobile; the child could not change its position; the legs were also entirely immobile; passive movements in all the joints were exaggerated. By putting the hands under the shoulders of the infant, the shoulders could be made to touch the ears of the patient.

Myotonic Status: All the muscles were hypotonic; no contractures were present.

Sensory Examination: There was no diminution of pain sensation; pricking with pin produced vigorous crying but no movements of any extremities.

Cranial Nerves: The optic nerves were normal, but the child seemed to suffer from cortical amaurosis. It was very difficult to determine, whether the

Fig. 4.—Case 6, boy, J. B.; Case 5, girl, E. P.

amaurosis was complete; at times it appeared that the infant followed a light; there was slight weakness of one external rectus. On account of the amaurosis, it was difficult to determine the mentality.

Progress: Gradual improvement in the motor powers was distinctly noticeable within the course of a few months; the infant learned to use its hands and to wiggle its toes.

Case 6.—*History.*—Joseph B., aged 14 months, was under observation since the age of 8 weeks. From birth the mother noticed that the infant never kicked around with its feet like other children. The patient was the youngest of three children. The infant was breast fed for one year. It had frequent attacks of bronchitis and died of pneumonia at 14 months. The family history was entirely negative. The mentality was normal.

Physical Examination.—When first seen, the infant could not use its legs at all; the arms, it moved but little, all deep reflexes were abolished; conjunctival

and pharyngeal reflexes were present. No electrical reactions were taken. There was gradual improvement in the motor power of the hands and feet. At 1 year the child could not yet sit up, nor hold its head upright, unsupported. The bowels were markedly constipated, and there was marked postural kyphosis when the child sat up. The muscles were all flaccid, soft and flabby. Movements at all the joints were exaggerated (on passive motion).

ETIOLOGY

In the great majority of cases myotonia is a congenital disease and the symptoms are manifest at birth; in the minority of cases the symptoms appear during the first year spontaneously or after some acute illness; in many of these cases the disease probably existed from birth, but the symptoms were not very marked and were probably not noticed until they became accentuated through some intercurrent disease. A review of the literature reveals that in the 136 cases reported the symptoms were noted at birth in most cases; during the first month in two cases; during the second month in seven cases; during the third in two cases; during the fifth in one case; during the sixth in five cases; during the eleventh month in one case; during the twelfth month in three cases; during the eighteenth month in one case, and not until walking time in one case. The diseases after which the symptoms of myotonia became manifest are: bronchitis, convulsions, diarrhea, pneumonia, measles and meningitis. In a number of cases the disease existed in a mild form at birth, but became aggravated by intercurrent disease (Beevor, Comby, Leclerc, Gastonguay and Duthoit).

Birth was premature in four cases (Bernhard, Courtney, Gastonguay, Concetti) and difficult in three cases; in a number of cases fetal movements were absent, or if present were weak and diminished in strength as pregnancy progressed; in many cases normal fetal movements were felt.

In 120 cases in which the sex was stated, sixty-four were males and fifty-six were females.

In 127 cases in which the age at time of report was stated, the distribution was as follows:

	Cases
From 0 to end of 1 year	51
From 1 to end of 2 years	21
From 2 to end of 3 years	18
From 3 to end of 4 years	13
From 4 to end of 5 years	7
From 5 to end of 6 years	8
From 6 to end of 7 years	2
From 7 to end of 8 years	3
From 8 to end of 9 years	1
From 9 to end of 10 years	1
From 10 to end of 11 years	0
From 11 to end of 12 years	1
From 12 to end of 13 years	1
Over 12 (50 yrs.)	1

The number of the pregnancy of which the patient was born was given in forty-three instances; the patient was:

The first born in nine cases
The second born in thirteen cases
The third born in eight cases
The fourth born in four cases
The fifth born in three cases
The sixth born in no case
The seventh born in three cases
The eighth born in one case
The ninth born in one case
The tenth born in one case

Thus, of forty-three cases, the patients were the offspring of early pregnancies (first three) in thirty cases (70 per cent.); it is evident that these figures contravert the accepted idea that this disease is due to reproductive exhaustion.

The family history was usually negative; the Wassermann reaction was positive in only two cases (Brunard and Gordon, both doubtful cases); it was negative in twelve cases (Cases, 131, 127, 116, 115, 110, 107, 106, 69, 57, 53, 50, 47); the Pirquet reaction was negative in nine cases. There was a history of alcoholism in the parents in two cases (Griffith and Concetti); in a few cases, relatives of parents were afflicted with neuromuscular diseases; in one of Collier's cases, the mother was always "weak in her legs"; in Silvestri's case, the aunt of the mother died of progressive muscular dystrophia; another infant had myxedoma, and another had osteomalacia. In a small percentage of cases the disease has been familial in character; Sorgente has reported two brothers suffering from the same disease; Concetti, a brother and a sister; Skoog, two in the same family; Foot, three in the same family; Beevor, four in the same family; Collier, two in the same family, and Reuben, three sisters, all of whom died.

There was a history of convulsions in five cases: Orbison's patient began to have convulsions at 1 year; Faber's patient, during first week of life; convulsions preceded death in both of Sorgente's patients; Brunard's patient had convulsions at 2 months, and in the case of Lereboullet, the flaccidity gave rise to rigidity during convulsions.

SYMPTOMS

Inspection.—Head: In two cases the head was asymmetrical.

Face: Many have noted that face was small in proportion to head; in a number of cases it was triangular in shape; in a small percentage of the cases there was a lack of mobility of facial expression; the face lacked individuality; it was doll-like and the lines which gave expression to the face were lacking; in a few cases the mouth was held open, and chin was constantly held on the sternum.

Neck: In two cases there were contractures of the sternocleidomastoid muscles present, so that the head was turned to one side.

Arms and Hands: In the typical cases the arms were held in a peculiar position; the arms were abducted; the forearms were flexed at elbow, and the hands were pronated so that the dorsum of the hands was in contact with the pelvic bones; in a few cases, the arms were abducted and the forearms were held in exaggerated supination (Zappert, Concetti, [two cases]); in several cases the arms were held in position of Erb's palsy; when contractures took place in the arms, the arms were abducted and elevated, the forearms were sharply flexed and the hands were pronated so that they came in contact with the chin (Kaumheimer).

Trunk: In prone position nothing abnormal was noted; in the sitting posture, almost all cases showed postural deformities of the spine (lordosis, scoliosis, kyphosis).

Chest: In fifteen cases, deformity of chest was noted; the most common deformity was lateral depression with elevation of the sternum; in a smaller number, there was anteroposterior flattening with excavation of the sternum (funnel shaped).

Abdomen: The abdomen was usually distended and appeared large in proportion to the chest; in twenty-eight cases the breathing was entirely abdominal and rapid (60 to 80 per minute).

Legs and Feet: In infants the thighs were partly adducted, the knees slightly flexed and the feet rotated outward; the feet were flat, long and pad-like in five cases (Charles, Gotti, Faber, Batten, Collier).

Abnormal Involuntary Movements. — Athetoid movements of the hands were noted in cases of Schippers, Cotteril, Haberman, Keersmaker, Brunard, Duthoit; tremor of the hands was noted in the cases of Purser and Snow; fibrillar twitchings, in the case of Gött; rotary movements of the head, in Feer's case, and of the hand, in Reuben's case; spasms were noted in the case of Guinon and Gauducheau (opisthotonus, a very doubtful case).

Tegumentary Status.—Vasomotor Status: Coldness and cyanosis of legs and feet were noted in three cases (136, 127, 22); marked vasomotor reactions in one case (70) and marked dermographia in one case (112); several writers have reported a marble-like mottling of the skin of the lower extremities.

Edema: Hard or soft edema was noted in thirteen cases; in the majority of cases it was confined to the feet and legs; in one case the edema extended to the forearms and face; in the majority of the cases it is a pseudoedema, due to adiposity and difficulty of differentiation of different tissues under the skin.

General Appearance: In the great majority of cases, the patients appeared well nourished, but on weighing them it was found that in nearly all cases they were underweight and undersized; all the infants weighed less than they appeared to weigh; there was excessive adiposity in ten cases, especially three cases of Concetti, Kundt and Rothmann (legs).

Palpation.—On palpation one found that one could not differentiate between panniculus adiposis, muscles and bones; one obtained the impression that all the tissues under the skin constituted one soft flabby mass; there was no infiltration of the muscles felt anywhere; the flabbiness of the muscles varied in degrees in different muscle groups; no atrophic muscles could be felt; the deposition of fat in subcutaneous tissues was normal and masked the muscles, which were diminished in size from disuse; in a small percentage of cases adiposity was marked, especially in the gluteal regions. In a small number of cases muscle thinness amounting to atrophy was present (two cases of Batten, Collier, Marburg, Archangelsky, Councilman, Thorspecken, Coombs, Schlivek, Gordon, Wimmer, Thompson).

Gastro-Intestinal Status.—Constipation was present in many cases, probably due to the involvement of the abdominal muscles; in a number of cases it was very obstinate and hard to relieve.

Respiratory Status.—The infants were very sensitive to affections of the lungs; in twenty-eight cases the intercostal muscles were entirely immobile, and the breathing was entirely abdominal; in these cases the breathing was very much accelerated, and in one case it was 90 respirations to the minute; in many more cases the intercostal muscles were only slightly affected.

The cardiovascular status was normal in every respect.

Rectal and vesical control was normal in all cases; in two cases there was involuntary passage of urine and feces, but there was no dribbling in either, probably due to lack of education; both of these patients were mentally backward.

Myatonic Status.—The chief symptom of this disease is hypotonia; the hypotonia varies in degree in different muscle groups; it may be so marked as to produce absolute immobility of limbs, trunk or head; it is usually most marked in the legs and least marked in the muscles innervated by the cranial nerves; it is usually widespread and affects all the skeletal muscles; all the muscle groups, however, are seldom affected to the same degree; no individual muscles in a muscle group are spared.

In not a single case was the muscular weakness absent in the lower extremities; in twelve cases the weakness was more marked in the arms; in patients under 1 year the muscles of the trunk and neck were

invariably affected. The involvement of the intercostal muscles has been mentioned. There was complete immobility of the chest noted in twenty-eight cases, and partial weakness in many more; there was weakness of the abdominal muscles in thirty-two cases; in older children there was marked improvement noted in the muscles of the arms, trunk, chest and neck; the muscles of the lower extremities showed the least tendency, and were the last to show marked improvement.

In the 128 cases in which the muscles affected were stated, the lower extremities were involved in every case; in only nine cases in which the lower extremities were affected, the upper extremities were not involved; in twelve cases the upper extremities were more affected than the lower; in thirty-one of the 128 cases, the trunk muscles were not affected; in thirty-seven of the 128 cases, the muscles of the neck were not affected or had recovered considerable power. The proximal muscles of the various muscle groups were usually more affected than the distal; in a small number the reverse was true; thus in the majority of cases there was more motor power in the toes and fingers than in the thighs and arms. The loss of power was never complete; thus in every case there was some power to move the toes and fingers, even when there was no power to move the arms, legs, trunk or head. The weakness was usually symmetrical; in cases of Zappert, Schippers, Faber and Bernhardt it was not.

In consequence of the muscular weakness, these children present a group of secondary symptoms. Weakness of the muscles of the head and neck leads to inability of holding the head upright without support and to inability to move the head in any direction; this depends on the degree of weakness of the muscles. Involvement of the muscles of the chest leads to diaphragmatic breathing and to the various deformities of the chest; when the abdominal muscles are involved, the abdomen is distended and constipation is very marked. When the arm muscles are affected, the children, when the weakness is very marked, cannot bring their hands to the mouth, only slight movements of the fingers being possible; in less severe cases, the arms can be elevated to the horizontal, but drop as if dead when the arms are elevated above the head. The legs usually show the greatest weakness; in the majority of infants only fine movements of the toes can be observed; the legs and thighs can be put in most grotesque and most uncomfortable positions, and these children are unable to correct these positions; as a result of the muscular weakness of the muscles of the feet, the feet are often long, narrow and flat, as are also the hands.

Involvement of the muscles of the spine makes it impossible for these patients to rise from the recumbent position; in older children, who have partly recovered, rising occurs in the step-ladder fashion of muscular dystrophia; when these children sit up, a number of postural

deformities become apparent, as lordosis, kyphosis and scoliosis; all these deformities usually disappear in the recumbent position.

Myasthenic Status.—The majority of these patients cannot sit up without support, or hold the head upright before the age of 2 to 4 years; the great majority do not learn to walk until they are 4 to 5 years old; in not a single case was normal walking possible; when walking is possible it is usually waddling in character, and steppage gait with ataxia is present. In cases where walking was not possible, progress was made by rolling over and over on the long axis of the body.

Of the cases reported in the literature, seventy-seven were over the age of 16 months; in these seventy-seven cases walking was possible in only thirteen cases. Walking was possible between:

14 months and 2 years in two cases (133, 73—doubtful cases)
2 years and 3 years in four cases (20, 39, 90, 118)
3 years and 4 years in two cases (37, 62)
4 years and 5 years in four cases (3, 42, 78, 88)
7 years and 8 years in one case (23)
12 years and 13 years in one case (94)
50 years and 51 years in one case (67)

As limited as are the movements at all the joints on active motion, as exaggerated are all the movements on passive; arms, legs and fingers can be placed in the most fantastic positions; in nearly all cases the legs can be crossed behind the back; flexion, extension, abduction, adduction and rotation are exaggerated at all the joints; they are only limited by the presence of muscular contractures; the contractures in this disease are due to unequal shortening of the various muscles.

Contractures.—These were present in thirty-seven cases, of which twenty-nine were in the lower extremities, six in the upper extremities and two in the sternocleidomastoid muscle; of the contractures in the lower extremities, sixteen were of the hamstring muscles and the knees, eight had talipes equinovarus, four of the hip and one of the back; of the six cases in which there were contractures in the upper extremities (Cases 1, 69, 77, 78, 79, 94), the contractures were usually most marked in the muscles which control the elbow; in most of these cases the arms were abducted, the elbows flexed and the hands were pronated.

In a few cases there were contractures present which could not be explained by any nerve distribution; as hyperextension of index fingers (51, 61), flexion of index finger (79) or flexion of middle fingers (108). In four cases, there were drop wrists, single or bilateral (1, 41, 51, 108).

Congenital Defects.—In addition to the six cases of congenital clubfoot which were present, there were two cases of umbilical hernia (Concetti, Cotteril); one case with double inguinal hernia (Charles); dislocation of right hip, malformation of right knee and partial luxa-

tion of left thumb (Cotteril); malposition of feet (Fletcher); genu recurvatum (Gastonguay); skull deformed in two cases (156, 51); thumbs dislocated (48); winged scapular in three cases; spina bifida (19); undescended testes and rudimentary penis (Concetti); mongolian idiocy (Concetti); dislocation of shoulder (Marburg); malocclusion of the jaws was present in two cases.

Bone Changes.—In nine cases Roentgen-ray examination of the bones was made; in only one case was there marked thinning of the long bones noted (Thorspecken); in one there was delayed ossification of the wrist centers; in seven, the bone findings were normal; in three cases, the Roentgen-ray pictures of the pituitary body were normal.

Evidence of slight rickets was found in six cases (Concetti, Beling, Feer, Marburg, Schüller, Purser).

Speech.—This was not affected; the children usually began to speak at the proper time; the teething was in no way affected; in fact, in a number of cases teething was early (speech defective only in Case 42).

Cranial Nerves.—The muscles innervated by the cranial nerves were affected in many more cases than was usually supposed. The optic nerves were atrophic in Case 56 (doubtful case); cortical amaurosis was present in Cases 91, 110, 123 (no changes in the optic nerves); ptosis was present in two cases (23, 73); the orbicularis palpebrarum was toneless in Case 39; ptosis, nystagmus and strabismus was present in Case 59 (very doubtful case); convergent strabismus was noted in Cases 59, 64, 91, 110, and nystagmus in three cases (72, 98, 124).

The face was involved in twenty cases (7, 22, 23, 30, 34, 45, 47, 51, 53, 73, 84, 95, 98, 106, 108, 109, 115, 117, 124, 128); the affection of the face showed itself in the complete absence of facial expression, and immobility of the muscles; there was a statuesque or doll-like appearance of the face, and lack of corresponding expression during crying or laughing; the mouth was open, and lower jaw drooped in four cases; drooling was present in two cases (42, 53).

Deafness was noted in two cases (59, 91); swallowing was difficult and nursing was impossible in sixteen cases (1, 2, 29, 40, 41, 43, 44, 53, 95, 106, 107, 108, 109, 122, 123, 136); in four cases the infants had to be forcibly fed; the voice and crying were feeble in seven cases (32, 48, 95, 106, 108, 109, 124); automatic movements of the muscles of mastication were present in one case (32).

The eyes were rather prominent in two cases (Collier and Wilson, Laffer).

Reflexes.—No definite statement can be made as to the presence or absence of the superficial or cutaneous reflexes; in the majority of

cases they were not tested; in about 60 per cent., in which they were examined, they were normal, and in 40 per cent. they were absent.

The deep or tendon reflexes were entirely abolished in eighty-four cases; they were present but feeble in twenty-one cases, and were normal or nearly so in thirteen cases (127, 126, 114, 91, 85, 83, 73, 55, 49, 39, 20, 17, 8). The Babinski sign was positive five times (118, 112, 99, 70, 51).

In few cases were the conjunctival and the pharyngeal reflexes absent; there is no uniformity of presence or absence of the superficial or deep reflexes; they may be present in the upper extremities and absent in the lower and vice versa; they may be diminished in one part of the body and normal in another; as a rule, the knee jerks are the most uniformly absent, and the conjunctival and the pharyngeal the most uniformly present.

In six cases (as the condition improved) there was a return of knee jerks, after complete absence from birth; in not a single case was there a disappearance of deep reflexes after they once returnd.

Electrical Reactions.—The electrical reactions were normal in fourteen cases (2, 3, 17, 22, 42, 45, 53, 55, 59, 67, 71, 85, 118, 123); there was diminished reaction to both galvanic and faradic currents in both nerve and muscle in fifty-two cases; there was diminished reaction to faradic current only in seventeen cases; to galvanic only, in six cases; there was no response to faradism in ten cases; no response to the galvanic current in three cases; there was no reaction to both currents in fourteen cases; in one case, there was normal reaction to faradism and diminished to galvanism, and in three cases there was normal reaction to galvanism and diminished to faradism.

In seven cases (four of which are doubtful) reaction of degeneration was found in some muscles; Rothman and Mittenheimer found partial reaction of degeneration in the lower extremities; Gött, Thorspecken, De Villa, Wimmer and Carcupino found reaction of degeneration in some muscles a few days before death.

The typical reaction in this disease seems to be a quantitative (not qualitative) diminution to both currents; greater diminution for the faradic than for the galvanic is usually present; almost every writer remarks on the ease with which these patients tolerate strong faradic currents.

Like the tendon reflexes, the electrical reactions are not the same in all muscle groups; they may be normal in upper extremities and diminished in lower extremities and vice versa; the muscles of the face most usually show normal reactions.

Sensory Examination.—It was usually normal; in twelve cases diminished sensation to needle pricks was noted; it was especially marked in six cases (1, 9, 25, 69, 127).

Mental Status.—Mentality was normal in sixty-one cases; in twenty cases mental backwardness was present, and in two, idiocy existed; a small number were noted to be precocious.

Metabolic Observations.—Gittings and Pemberton found that in this disease the creatinin shows a great departure from normal controls, and that there is no marked evidence of disturbance in the calcium metabolism. (The experiments were carried out on the case reported by Griffith.)

Lumbar Puncture.—The spinal fluid was examined in three cases and was normal in all (Skoog, two cases; DeVilla); the blood was examined in two cases and was also normal.

COURSE OF THE DISEASE

In the great majority of the congenital cases, the progress is one of slow but gradual improvement; however, in not a single case was there complete recovery; in the cases in which the symptoms became manifest quite suddenly after an acute illness, improvement was usually more rapid than in the former group of cases. In a small minority of cases (thirteen cases: 133, 107, 108, 109, 85, 43, 44, 36, 41, 26, 5) there was no improvement noted at any time; in these cases there was progressive deterioration up to death. In some of the cases in which there was progressive improvement, there were noted long periods in which the condition was stationary, and then they gradually improved or deteriorated. In a small number of cases, after certain motor accomplishments had been attained, they were lost and regained in the future (in certain instances). The patient of Schüller was able to sit and stand at 10 months, and was no longer able to do either at 12 months; the patient of Haberman could no longer sit up after he had been able to do so; in Case 26 the patient, at 18 months, could creep and later could not; in Case 113, the patient, at 9 months, could sit and stand, and gradually ceased both; in Case 10 the patient sat up at 7 months, and at 11 months had lost this power; the patient of Berti, at 3 years, began to grasp toys and to move the legs somewhat; this it did until it was 5 years old; there was no further improvement for some time, and then suddenly the patient was able to move about and to stand.

PROGNOSIS

The prognosis as to recovery is absolutely bad; there is no record of complete recovery in a single case. Of eighty-four cases, in which

the final outcome was stated, forty-five are known to have died; of these:

Twenty-five died between birth and 6 months of age
Four died between 6 months and 1 year of age
Four died between 1 year and 2 years of age
One died between 2 years and 3 years of age
Three died between 3 years and 4 years of age
Three died between 5 years and 6 years of age
Five, age of death unknown

Of the deaths:

In thirty-two death was due to bronchopneumonia
In five cause of death was unknown
In one death was due to choking fit
In three death was due to convulsions
In one death was due to fever (?)
In one death was due to attack of cyanosis
In one death was due to diphtheria

From these statistics it becomes apparent why there are so few cases reported in older children; of forty-two infants of whom the final outcome was known at time of report, twenty-nine are known to have died before the age of 1 year (a mortality of about 70 per cent.). One cannot understand why it is, in the face of these statistics, that many writers give such a favorable prognosis in this disease.

TREATMENT

In a disease in which there is a natural tendency for a certain amount of improvement to take place, it is hard to judge the effect of treatment; in certain cases there is no improvement brought about by measures which seem to have caused marked improvement in others. I have tried thyroid in every case without the slightest effect; others have reported good results from thyroid and epinephrin; faradism, galvanism, exercise, massage and corrective measure applied to the contracted muscles are indicated. In older children, general tonics, cod liver oil and especially strychnin may be of service.

PATHOLOGY

In studying the pathologic findings we find that the central nervous system was normal in the cases of Baudouin and Lereboullet, Spiller, Brunard, Councilman and Dunn (only very slight changes).

There was remarkable concordance in the pathologic findings of Baudouin, Collier and Holmes, Rothmann, Marburg, DeVilla, Foot, Griffith, Kaumheimer and Concetti; these found pathologic changes in the anterior horn cells, in the fibers which emanate from these cells and from the peripheral nerves, and they have traced the same changes into the muscles and into other organs (thymus and thyroid). In the cases of Baudouin, Collier and Holmes, and Rothmann, the lesions

showed absence of all inflammatory signs, and mostly spoke for a simple arrested development; in the case of Marburg, there was evidence of true destruction (vacuolation, intense sclerosis and fragmentation of the cylinders).

Sclerosis of the thymus was found in the cases of Spiller, Councilman, Rothmann, Baudouin and Pollak, and the thyroid was affected in the cases of Berti, Spiller, Baudouin, Concetti and Pollak.

CEREBRUM

The following writers have found noteworthy pathologic lesions either in the cerebrum or in the nuclei of the cranial nerves. Baudouin found the cells of the nuclei of the sixth and the twelfth cranial nerves in a state of chromatolysis. Collier and Holmes found pathologic changes in the nuclei of the hypoglossal and the ambiguus nerves. Griffith found the brain unusually large, and the cells of the hypoglossal nucleus were diminished in number; the pia was edematous. Kaumheimer found an increase of glia in the cerebrum, medulla and cord; pathologic changes were also found in the cells of the nuclei of the hypoglossal and the ambiguus nerves. Rothman found at the nucleus of the hypoglossal marked development of the blood vessels, the cells were degenerated and there was a diminished number of motor cells in the nuclei; the same was true in the vagus nucleus; in the height of the pyramidal tracts, there was still more marked absence of motor ganglion cells; the cerebellum was small. Berghinz found hypoplasia and microgyria of the cerebrum; the nerve cells of the cerebellum were small. Concetti found all layers of the cerebrum reduced in volume, and the Purkinje cells of the cerebrum were few and altered in shape.

SPINAL CORD

With the exception of those cases in which there were no lesions found in the cord, the findings were fairly uniform; the anterior roots were reduced in size and contained many fibers deficient in myelin; the posterior roots were usually of normal size (except in Rothmann's case); the number of cells in the anterior horns was decreased, and there was an absence of the large ganglion cells (Archangelsky). The cells which were present were of irregular shapes and usually of smaller caliber than normal cells; a number of these cells showed pyknosis or vacuolation.

Changes in the cells of Clarke's columns were found by Rothmann, Archangelsky, Kaumheimer and Marburg; the cord columns occasionally showed deficient myelinization; an increase in the neuroglia of the cord was found by Kaumheimer, Foot, Rothmann and Marburg; the nerve fibers in the cord were diminished in number and lacked myelinization (Archangelsky).

TABLE 1.—SUMMARY OF—

Author	No.	Sex	Age	No. of Pregnancy	Muscles Affected				Cranial Nerves	Tendon Reflexes
					Legs	Arms	Trunk	Neck		
Archangelsky and Abrikosoff	1	♀	3½ mo.	.....	++	+	+	+	Swallowing affected	Abolished
Ashby	2	♀	8 yr.	.....	++	+	+	+	Swallowing affected	Abolished or weak
Ausset	3	♀	2¾ yr.	.....	++	+	+	+	.....	Feeble
Baudouin	4	♀	4 mo.	.....	+	+	+	+	.....	Abolished
Batten	5	♀	6 yr.	10th	+	+	+	+	.....	Abolished
	6	♂	6 yr.	3d	+	..	+	+	.....	Abolished
	7	♂	7 yr.	9th	+	+	+	..	Face expressionless	Abolished
	8	♂	6 yr.	.....	+	+	+	..	.....	Present
Beling	9	♂	3½ yr.	3d	+	+	+	+	.....	.....
Beevor	10	♀	20 mo.	.....	++	+	+	..	.....	Abolished
Berghinz	11*	..	.....	.....	..	..	..	..	.....	.....
Bernhard	12	♂	9 mo., premature	.....	++	+	..	+	.....	.....
Berti	13	♀	5 yr.	.....	++	+	..	..	.....	Feeble
	14	♂	3 days	.....	+	+	+	+	.....	Abolished
Bienfait	15	♂	12 mo.	.....	+	+	+	+	.....	Feeble
Bing	16	♂	3½ yr.	.....	++	+	+	..	.....	Abolished
Brunard	17	♀	2 yr.	.....	+	+	+	..	.....	Knee jerks present
Carcupino	18	♀	3½ mo.	.....	+	+	+	+	.....	Diminished or abolished
Cattaneo	19	♀	4 mo.	.....	+	+	+	+	.....	Abolished
Charles	20	♂	6 yr.	1st	++	+	+	..	.....	Knee jerks present
Chéné	21	♀	6 mo.	.....	+	+	+	+	.....	Abolished
Collier and Wilson	22	♂	4¼ yr.	2d	++	+	..	..	Mastication affected; face affected	Abolished
	23	♂	7 yr.	1st	+	++	+	..	Facial muscles weak; unable to close eyes completely	Abolished
	24	♂	5¼ yr.	5th	++	+	..	..	.....	Abolished or feeble
	25	♀	1¾ yr.	1st	++	..	..	..	.....	Abolished
Collier and Holmes	26	♂	3½ yr.	5th	+	+	+	+	.....	Abolished
Collier	27	♂	5 yr.	.....	++	..	..	..	.....	Feeble
Comby	28	♂	8 yr.	.....	+	+	+	+	.....	Abolished
	29	♂	4 mo.	.....	++	+	+	+	Difficulty in swallowing	Abolished

* No clinical details.

—THE LITERATURE

Electrical Reactions	Contractures	Mentality	Progress	Cause of Death	Necropsy Biopsy	Remarks
No response to faradic	Equinovarus; arms	Normal	Died	Pneumonia	+	Chest deformed; abdominal breathing; diminished pain sensation; double wrist drop
Normal	.....	Backward	Improvement			
Normal	.....	Normal	Improvement	.....	.....	Could take a few steps at 4 years
No response to faradic	.....	Normal	Improvement	Pneumonia	+	Abdominal breathing
.....	Knees, hips	Normal	No improvement; died	?		
Diminished to faradic; absent to galvanic	.....	Normal	Died	?		
Diminished to faradic	Legs	Normal				
Diminished to faradic	.....	.....	Improvement	.....	.....	Marked lordosis
.....	Knees	Normal	.....	.....	.....	Pain sensation diminished
Persistent to violent current; diminished	.....	Normal	Improvement	.....	.....	Onset at 12 months after a bronchitis; later tendon reflexes returned
.....	.....	.....	.....	.....	+	Necropsy
No response to faradic; diminished galvanic	.....	.....	.....	.....	.....	Premature birth; kyphoscoliosis
Diminished faradic	.....	Normal	Improvement	.....	.....	Hard edema of legs
Diminished faradic or absent	.....	.....	Improvement	.....	.....	Abdominal breathing
.....	.....	Backward	Improvement			
Faradic normal; galvanic diminished	.....	.....	Improvement			
Electric reactions not diminished	.....	Idiot	Improvement	.....	.....	Athetosis of hands; normal at birth; convulsions at 2 months; syphilitic keratitis
Diminished or absent	.....	.....	Improvement; died	Pneumonia	.....	Reaction of degeneration in muscles before death
Diminished to both	.....	Normal	.....	.....	.....	Kyphosis; abdominal breathing; hard edema of feet; spina bifida
Diminished faradic	.....	.....	.....	.....	.....	Began to walk at 2 years; convulsion at 1 year; kyphosis; flat feet, long and narrow
Diminished to both	.....	Normal	Improvement	.....	.....	First noticed at end of second month
Normal faradic galvanic diminished	Hip, knee	Normal	Improvement	.....	.....	Legs cold, blue; kyphosis; flat feet
Diminished to faradic	Legs	Normal	Improvement	.....	.....	Later could walk a little
Diminished to faradic, normal to galvanic	Thighs, feet	Normal	Improvement; died at 7 years	Pneumonia	+	Kyphosis; onset at 6 months
Diminished but present	Hips	Fair	Improvement	.....	.....	Well until 12 months; onset followed bronchitis; diminished sensation to pain
Diminished faradic	Thighs, calfs	Normal	No improvement	.....	+	At 18 months could creep; later could not; kyphosis
Diminished faradic	.....	.....	Improvement			
.....	.....	Normal	.....	.....	.....	Kyphosis; could not walk
Diminished excitability	.....	Normal	Improvement	.....	.....	Onset at 1 month after diarrhea; kyphosis

TABLE 1.—SUMMARY OF—

Author	No.	Sex	Age	No. of Pregnancy	Muscles Affected				Cranial Nerves	Tendon Reflexes
					Legs	Arms	Trunk	Neck		
Concetti.....	30	♂	10 wk., premature	7th	+	+	..	..	Facial immobility	Abolished
	31	♂	7 mo.	2d	+	+	+	+	.....	Abolished
	32	♀	8 mo.	.....	+	+	+	+	Voice feeble; automatic movements of mastication	Abolished
	33	♀	.....	1st	+	+	+	+	Extremely fat	.....
	34†	♂	2 mo.	2d	+	+	+	+	Face apathetic	.....
	35	♂	6 mo.	.....	++	+	..	..	Adipose tissue abundant	Abolished
	36	♀	4½ mo.	.....	+	+	+	+	.....	.....
	37	♀	3 yr.	.....	++	+	..	..	Father alcoholic; adipose tissue abundant	Feeble
	38	♀	53 days	.....	++	+	+	+	.....	Abolished
Coombs.....	39	♀	10 yr.	.....	+	++	+	..	Orbicularis palpebrarum; flat, toneless	Present in lower; absent in upper
Cotteril.....	40	♀	2½ yr.	4th	++	+	+	+	Could not suck; face vacant; mouth open; eyelids droop	Abolished
Counellman and Dunn	41	♂	6 mo.	2d	+	++	+	+	Swallowing difficult	Abolished
Courtney and Eaton	42	♂	5½ yr.	.....	++	+	+	+	.....	Abolished
Dunn.....	43	♂	5 mo.	2d	+	+	+	+	Nursing difficult	Abolished
	44	♀	5 mo.	2d	+	+	+	+	Lost power of sucking; could not swallow	Abolished
Dutholt.....	45	♀	2 yr.	.....	+	+	+	+	Face atonic	Abolished
Feer.....	46	♀	4½ mo.	.....	++	+	+	+	.....	Abolished
Fletcher.....	47	♂	3 yr.	4th	+	+	+	+	Face expressionless	Feeble
Foot.....	48	♂	3½ mo.	8th	+	+	..	..	Cry feeble	Feeble
Faber.....	49	♂	29 mo.	3d	+	..	+	+	.....	Pronounced
	50	♂	8 wk.	2d	++	+	..	..	.....	.....
	51	♂	30 mo.	2d	++	+	+	+	Expression inert skull peculiar in shape	Abolished
Fieves.....	52‡									

† Brother of No. 33.
‡ Details not obtainable.

—THE LITERATURE—(*Continued*)

Electrical Reactions	Contractures	Mentality	Progress	Cause of Death	Necropsy Biopsy	Remarks
Diminished	.....	Normal	Improvement; died	Pneumonia	.....	Kyphosis; abdominal breathing; arms supinated
.....	.....	Backward	Improvement; died	Pneumonia	.....	Edema of legs (hard); kyphosis; testes undescended; penis rudimentary
.....	.....	Backward	Improvement; died	.....	.....	Mongolian facies; general pseudo-edema; adiposity
.....	.....	.....	Died at 3 months	Pneumonia	.....	Patient not seen; history from parents
.....	.....	.....	Improvement; died at 5 months	Pneumonia	.....	Hard edema of calves, thighs and forearms; abdominal breathing
.....	.....	Backward	.....	.....	.....	Lordosis
.....	.....	.....	Died; no improvement	Bronchial pneumonia	.....	First noticed at 2 months; signs of hypothyroidism; umbilical hernia; firm edema; constipation
Diminished to faradic and galvanic	.....	Backward	Improvement	.....	.....	Kyphosis; constipation; walked at 3 years with support
Diminished to faradic and galvanic	.....	.....	Died at 2 months	Pneumonia	.....	Arms abducted and supinated; kyphosis; thorax deformed; abdominal breathing
Diminished to faradic and galvanic	.....	.....	Improvement	.....	.....	Began to walk at 2½ years; onset at 12 months
Slightly dim to faradic and to galvanic	Sternocleidomastoid; left hand; club foot; equinovarus	Backward	.....	.....	.....	Constipated; incontinence of urine and feces; umbilical hernia; winged scapulae; pectus excavatum; thumbs dislocated; right hip dislocated; athetoid movements
.....	.....	Normal	Improvement and later worse; died	Choking fit	+	Drop wrist onset at 3 weeks; chest deformed; abdominal breathing
Normal	.....	Normal	Improvement	.....	.....	Speech defective; premature; reflexes returned; drooled; walked
.....	.....	Normal	Progressively worse; died	Pneumonia	.....	Abdominal breathing
....	.....	Normal	Worse; died	Pneumonia	.....	Abdominal breathing; chest deformed
Diminished galvanic in legs; normal in arms; diminished faradic	.....	Normal	Improvement	.....	.....	Abdominal breathing; kyphosis; athetoid movements
Diminished to faradic and galvanic	Equinovarus	Normal	Slow improvement	.....	.....	Rotatory movement of head; hands pronated; abdominal breathing
Diminished to faradic	Knee	Normal	.....	.....	.....	Wassermann negative
Diminished to faradic and galvanic	.....	.....	Died	Pneumonia	.....	Thumbs dislocated; first and second children born paralyzed and died at 6 months and 9 weeks, respectively
Diminished to faradic and galvanic	.....	Backward	.....	.....	.....	Convulsions in first week; no paralysis until walking time; tendency to adduct thighs; kyphosis
Faradic absent; galvanic normal	.....	.....	.....	.....	.....	Cesarean section; Wassermann negative; hands pronated; arms abducted
Diminished to faradic and galvanic	.....	Normal	No improvement	.....	.....	Onset at 3 months; funnel chest; abdominal breathing; kyphosis; index finger hyperextended; drop wrist; Babinski reflex present

TABLE 1.—SUMMARY OF—

Author	No.	Sex	Age	No. of Pregnancy	Muscles Affected				Cranial Nerves	Tendon Reflexes
					Legs	Arms	Trunk	Neck		
Fearnsides	53	♂	3½ yr.	.....	+	+	+	+	Muscles of face and jaw feeble; face flat	Abolished
Gastonguay	54	♀	3¾ yr.	3d	+	+	+	+	.....	Abolished
Gatti	55	♂	2 yr.	.....	++	+	..	..	.....	Normal
Gordon	56§	♀	2 yr.	.....	+	+	+	+	Optic nerves atrophic	Abolished
	57	♀	3 yr.	.....	+	+	+	+	.....	Feeble
Griffith	58	♂	15 mo	.....	+	+	+	+	.....	Abolished
Guinon and Gaudueheau	59	?	?	.....	+	+	+	+	Ptosis; nystagmus; strabismus; deafness	Abolished
Guillemot	60	?	18 mo	.....	+	+	+	+	.....	.....
Gött	61	♂	2½ yr.	.....	+	+	+	+	.....	Abolished
Haberman	62	♀	3½ yr.	.....	++	..	..	..	.....	Abolished
	63	..	4 mo.	.....	+	+	+	+	.....	Abolished
	64	♀	18 mo.	.....	+ athetoid movements	+	+	+	Converging strabismus	Abolished
Hertz and Johnson	65	♂	3½ yr.	.....	+	+	+	+	.....	Abolished
Hummel	66	♂	3 yr.	.....	++	+	+	+	.....	Abolished
Hartenberg	67	♀	50 yr.	.....	++	..	..	..	.....	Feeble
Jovane	68	♂	3 mo.	.....	+	+	..	..	.....	Abolished
Kaumheimer	69	♀	3¾ mo.	.....	+	++	+	+	.....	Abolished
Keersmaker	70	♂	.....	7th	+	+ Athetoid movements	+	+	.....	Abolished; Babinski reflex present
Kundt	71	♀	18 mo	.....	+	..	..	..	.....	Abolished or diminished
Koch	72	?	15 mo.	2d	+	++	++	+	Nystagmus	Feeble
Laffer	73	♀	8 yr.	1st	+	+	..	..	Face immobile; drooping of eyelids	Present
Leclerc	74	♀	4 yr.	4th	+	+	+	+	.....	Abolished
Lereboullet and Baudouin	75	♂	11 mo.	2d	+	+	++	+++	.....	Diminished
Lungenbühl	76	♀	5 mo.	.....	++	+	+	+	.....	Abolished
Marburg	77	♂	3 mo.	7th	+	++	+	+	.....	Abolished
	78	♀	6 yr.	.....	+	+	+	..	.....	Abolished

§ Colored.

—THE LITERATURE—(*Continued*)

Electrical Reactions	Contractures	Mentality	Progress	Cause of Death	Necropsy Biopsy	Remarks
Normal	Adductors of thigh	Backward	.....	.....	.....	First noticed at 6 weeks; drooled; knee jerks returned; kyphosis; Wassermann negative
.....	.....	.....	.....	.....	.....	Premature; genu recurvatum
Normal	.....	.....	Improvement	.....	.....	Flat feet
Diminished to faradic and galvanic	Equinovarus	Backward	Improvement	.....	.....	Skull peculiar; Wassermann positive
Diminished to faradic and galvanic	.....	Fair	Improvement	.....	.....	Wassermann negative
Absence of all faradic and galvanic response	Slight contracture	.....	Improvement; died	Pneumonia	+	Abdominal breathing
Normal	.....	.....	.....	.....	.....	Transient hypertonicity; exaggerated extension of head; subluxation of inferior maxilla
.....	.....	.....	Improvement	.....	.....	Reported in discussion of Comby's case
Diminished to faradic and galvanic; partial reaction of degeneration	.....	Normal	No improvement and no worse; died	Pneumonia	+	Both index fingers overextended; fibrillary twitchings in hands
Total loss in some muscles, diminished in others	.....	Normal	Died	Unknown	.....	Walked with support
Diminished to both	.....	Normal	.....	.....	.....	Lordosis
Diminished to both	.....	Normal	.....	.....	.....	First noticed in sixth month; could not hold head up, which it could before; constipation; abdominal breathing
.....	.....	Normal	Improvement	.....	.....	Scoliosis
Diminished to both	.....	Normal	.....	.....	.....	Kyphosis
Normal	.....	.....	.....	.....	.....	Scoliosis; married; mother of a son; walked
Diminished to faradic; absent to galvanic	.....	.....	Died at 5 months	Pneumonia	.....	Abdominal breathing
Diminished to both	Arms	Normal	Died	Pneumonia	+	Arms elevated; flexed; pronated; flat feet; chest deformed; sensation diminished; Wassermann negative
Diminished to both	.....	.....	Improvement	.....	.....	Kyphosis; abdominal breathing; marked vasomotor reactions; Wassermann negative
Normal, only slightly diminished	.....	Normal	Improvement	.....	.....	Roentgen ray of bones normal
Diminished to both	.....	Normal	.....	.....	.....	Onset at 6 months
Greatly diminished to faradic	.....	Normal	.....	.....	.....	Walked at 14 months; lordosis
Diminished	.....	Backward	Slow improvement	.....	.....	Onset at 7 weeks after pneumonia; hard edema of legs
.....	.....	.....	Died	Convulsions	.....	Convulsive fits; hard edema
No response to faradic and galvanic f	.....	.....	Improvement	.....	.....	Abdominal breathing
	Arms	Normal	Died	Pneumonia	+	Onset at 6 weeks; funnel-shaped sternum
Diminished to both	Thighs; legs; equinus elbows	Normal	.....	.....	+	Walked since age of 5 years, erect position

TABLE 1.—SUMMARY OF—

Author	No.	Sex	Age	No. of Pregnancy	Muscles Affected				Cranial Nerves	Tendon Reflexes
					Legs	Arms	Trunk	Neck		
Mensi	79	♀	12 days	.....	..	++	..	..	.....	.....
	80	♂	4 days	.....	+	+	..	..	.....	.....
	81	♂	2 days	.....	++	+	+	..	.....	.....
	82	♀	1½ mo.	.....	+	++	..	..	.....	Absent
	83	♀	At birth	.....	+	++	+	+	.....	Plantar patella present
Moussous and Carles	84	♀	4½ yr.	.....	+++	++	..	..	Face inert	Abolished
Muggia	85	♀	4 yr.	.....	++	+	..	..	.....	Normal (feeble)
Mettenheimer, Götzky and Weihe	86	?	8 mo.	.....	+	+	..	..	.....	.....
	87	?	5 mo.	.....	+	+	+	+	.....	.....
Naish	88	♂	4½ yr.	.....	+	++	+	+	.....	Just present
Ollari	89	♀	70 days	.....	+	+	+	+	.....	Abolished
Openshaw	90	♂	7½ yr.	.....	+	+	..	+	.....	Abolished
Orbison	91	♀	4 yr.	3d	+ Could not walk	+	+	+	Could not see well or hear acutely; strabismus	Present
Oppenheim	92¶	..	.....	.....	+	+	+	+	.....	Abolished
	93	♀	19 mo.	.....	+	+	..	..	.....	Abolished
	94	♂	12 yr.	.....	+	+	+	..	.....	Abdominal reflex absent; feeble
Pollak	95	♂	4 mo.	.....	+	+	+	+	Weak voice; face muscles; swallowing affected; hypoglossal nerve involved	Abolished
Pelz	96	..	1¼ yr.	.....	..	..	..	..	.....	.....
Princeteau	97#									
Purser	98	♂	2¼ yr.	.....	++	+	+	+	Nystagmus; facial muscles somewhat affected	Abolished
Reiner	99(1)	♀	3 yr.	.....	+	+	+	+	.....	Abolished; Babinski reflex positive
	99(2)	♂	11 mo.	.....	+	+	+	+	.....	Diminished
Reyher and Helmholtz	100	..	.....	.....	..	..	..	..	.....	.....
Rosenberg	101	♂	2½ yr.	.....	++	..	..	..	.....	Abolished
Rothmann	102	?	5 mo.	1st	++	+	..	..	.....	Abolished
Rocher	103**									
Rad	104††									
Rietschel	105‡‡	?	4 yr.	.....	..	..	..	..	.....	.....
Reuben	106	♀	5½ mo. Premature	1st	+	+	+	+	Difficulty in swallowing; face immobile; voice weak	Abolished
	107§§	♀	3 mo.	1st	+	+	+	+	Difficulty in swallowing	Abolished
	108§§	♀	6 mo.	2d	+	+ Rotatory movement of rt. hand	+	+	Difficulty in swallowing; sensation diminished; face immobile; feeble voice	Abolished
	109§§	♀	10 wk.	3d	+	+	+	+	Difficulty in swallowing; sensation diminished; feeble voice	Abolished

¶ Four cases.
# In discussing the case of Moussouns, he said he had seen a case. No details were obtainable.
** In discussing case of Moussons, stated he had seen a case; no details.
†† Festschrift des Cnappechen Kinderspitals, Neuremberg, 1914. No details were obtainable.
‡‡ No details.
§§ Sisters.

Electrical Reactions	Contractures	Mentality	Progress	Cause of Death	Necropsy Biopsy	Remarks
.....	Slight contracture	.....	Died	Pneumonia	+	Flexure of forearm, arms and fingers
.....	.....	.....	Died 27 days	Pneumonia	+	Edema of feet and legs
.....	.....	.....	Died 2 months	Pneumonia	+	
.....	.....	.....	Died	Pneumonia	+	Edema of arms and legs
.....	.....	.....	Died 3 weeks	Pneumonia	+	Hemorrhage into suprarenal capsules
Diminished to both	.....	Backward	.....	.....	.....	Could not walk or stand
Normal	.....	.....	No improvement			
.....	.....	.....	Died	Pneumonia	+	
Partial reaction of degeneration in lower extremities	.....	.....	Died	Pertussis and pneumonia	+	
Diminished to both	.....	Normal	.....	.....	.....	Walked since age of 4 years; flat feet
Diminished to faradic	.....	Normal	Improvement			
Diminished to faradic and normal galvanic or	Hips	Normal	.....	.....	+	Onset at 18 months after measles; began to walk at 2½ years
Diminished to faradic	Hamstring	Backward	.....	.....	.....	Normal up to 6 months; convulsions at 1 year; hands and feet long
Diminished or absent	.....	Normal	Improvement			
Absent except in peroneus	.....	Normal	Improvement			
Diminished	Knee; back; biceps	Normal	Stationary; later worse	.....	.....	Could not walk
No reaction to galvanic or faradic	.....	.....	Improvement; died	Bronchitis	+	Kyphosis; abdominal breathing; constipation; necropsy not reported
.....	.....	Idiot				
Absent	.....	Normal	Improvement			
Diminished to both	.....	Normal	Improvement	.....	.....	One of twins
Diminished	.....	Normal	Improvement			
.....	.....	Died	?	?	+	
Absent or diminished	Hamstrings	Normal	Improvement	.....	.....	Sat up at 7 months; first noticed at 11 months
Absent or diminished	.....	Normal	Died at 5 months	.....	+	Reaction of degeneration in some muscles
.....	.....	.....	Improvement			
Absence of faradic response; galvanic diminished	.....	Normal	Improvement	.....	.....	Abdominal breathing; Wassermann negative; normal roentgen-ray development
.....	.....	Normal	No improvement; died	Pneumonia 4 months	.....	Wassermann of mother negative; abdominal breathing
Diminished to both	Sternocleidomastoid	Normal	Improvement; died	Pneumonia 10 months	.....	Drop wrist; chest deformed; abdominal breathing; roentgen ray normal
Diminished to both	.....	Normal	No improvement; died	Pneumonia 4 months	.....	Chest deformed; abdominal breathing

TABLE 1.—SUMMARY OF—

Author	No.	Sex	Age	No. of Pregnancy	Muscles Affected				Cranial Nerves	Tendon Reflexes
					Legs	Arms	Trunk	Neck		
Reuben	110	♀	8 mo.	2d	+	+	+	+	Strabismus; amaurosis	Abolished or feeble
	111	♂	14 mo.	3d	+	+	+	+	.....	Abolished
Schippers	112	♂	2 yr.	.....	++	..	..	..	.....	Babinski positive
Schüller	113	♂	19 mo.	.....	++	+	..	+	.....	Abolished or feeble
Schlivek	114	♀	2¼ yr.	1st	+	++	..	..	.....	Normal
Skoog	115	♂	6 yr.	3d	+	+	+	+	Muscle of jaw and tongue affected; jaw drooped	Abolished
	116¶¶	♂	4 yr.	4th	+	+	+	+	.....	Abolished
	117	♀	22 mo.	.....	+	+	+	+	Face affected	Abolished
Snow	118	♂	2¾ yr.	5th	++	Tremor of hands	..	..	.....	Abolished; Babinsi present
Sorgente	119	♂	27 days	.....	+	+	..	..	.....	Abolished
	120‖	♀	5 days	.....	+	+	..	..	.....	.....
Simonini	121	♀	10 mo.	.....	++	+	+	+	.....	Feeble
Silvestri	122	♂	45 days	.....	+	+	+	+	.....	Abolished
Spiller	123	♂	22 mo.	.....	+	++	..	..	Amaurosis; strabismus; could not swallow	Absent
Strauch	124	♀	6 mo.	2d	+	+	+	+	Cry feeble; face affected nystagmus	Abolished
Sutherland	125	♂	2 yr.	.....	+	+	+	+	.....	Abolished
Thompson	126	♀	14 mo.	3d	+	+	+	+	.....	Present
Thorspecken	127	♀	4½ yr.	.....	++	+	+++	+	.....	Absent in lower, present in upper
Tobler	128	♂	1¾ yr.	1st	+	+	+	+	Facial muscles inactive	Abolished
Variot and Chatelin	129	♀	3½ yr.	.....	++	+	+	..	.....	Abolished
Variot and DeVillers	130	♀	6 mo.	.....	+	+	+	+	.....	.....
de Villa	131	♂	3 yr.	.....	+	+	+	+	.....	Abolished
	132	♀	3 yr.	2d	+	+	+	+	.....	Abolished
Wynter	133	..	15 mo.	.....	+	+	+	+	.....	?
Zahorsky	134	♂	2½ yr.	.....	+	+	+	+	.....	Diminished
Zappert	135	♂	6½ mo.	.....	++	+	+	+	.....	Abolished
Wimmer	136	♂	16 mo.	.....	+	+	+	+	Could not nurse	Abolished

¶¶ Brother of No. 115?
‖ Sister of No. 119.

—THE LITERATURE—(*Continued*)

Electrical Reactions	Contractures	Mentality	Progress	Cause of Death	Necropsy Biopsy	Remarks
No response to faradic; diminished to galvanic		?	Improvement	.....	.....	Wassermann of mother negative; chest deformed; funnel chest
.....	.....	Normal	Improvement; died at 14 months	Pneumonia		
Diminished to both	.....	.....	Improvement	.....	.....	Athetoid movements of fingers; marked dermographia
Diminished to both	.....	.....	.....	.....	.....	At 9 months could sit and stand; gradually ceased both
Diminished to both	.....	Normal	Improvement	.....	.....	Arms in position of Erb's paralysis
Diminished to both	.....	Normal	Improvement	.....	+	Wassermann negative
Diminished to both	.....	Normal	Improvement	.....	+	Wassermann negative
Absent or diminished to both	.....	Normal	Improvement	.....	+	
Normal or diminished	.....	Backward	Improvement	.....	.....	Onset at 2 months after meningitis ? kyphosis; walked at 3 years
Absent to both	.....	.....	Improvement; died at 1 month	Bronchitis and convulsions	.....	Abdominal breathing
.....	.....	.....	Died at 15 days	Convulsions		
Diminished	.....	.....	.....	.....	.....	Abdominal breathing
Faradic absent	.....	.....	Marked improvement in 4 months	.....	.....	Treated with suprarenal extract
Normal in legs	.....	.....	Improvement; died	Fever ?	+	First noted at 5 months
Absent	.....	Normal	Improvement; died	Attack of cyanosis	+	Abdominal breathing; constipation; edema of feet
.....	.....	Backward				
Diminished to both	.....	Normal	Great improvement	.....	.....	First noticed at 3 months
Diminished to both; reaction of degeneration in some muscles	Club foot	Normal	Improvement	.....	.....	Sensation diminished; legs cyanotic and cold; bone of legs atrophic; flat feet; Wassermann negative; chest deformed
Diminished or absent	.....	Normal	Improvement; died	Diphtheria	.....	Kyphosis
Diminished to both	Hip	Normal	.....	.....	.....	Symptoms noted at 6 months
.....	.....	.....	Died	Pneumonia at 6 months	+	Kyphosis; no report of necropsy
Diminished to both	.....	.....	Died	Pneumonia	.....	Abdominal breathing; Wassermann negative; lumbar puncture
Diminished; certain contractions slow	.....	.....	Improvement	.....	.....	Normal
No response to faradic	.....	Normal	Grew worse	.....	.....	Child could walk
No response to electricity						
?	Talipes equinus	.....	.....	.....	.....	Arms elevated and flexed at elbows; supination of arms; abdominal breathing
Diminished to both; beginning reaction of degeneration	Talipes varus	Normal	Progressive	.....	.....	Feet cyanotic; atrophy marked in this case

The nerve roots were small and very slender. Councilman found slight degeneration in the myelin of the posterior columns, anterior and posterior nerve roots and in the spinal ganglia. DeVilla found slight rarefaction of the pyramidal bundles. Foot noted marked gliosis in the anterior horns. Gliosis was found by Kaumheimer, Marburg, Rothmann and Foot (especially in the anterior horns).

MUSCLES

The gross appearance of the muscles has been compared by Foot to that of raw pork; the muscle is usually thin, pale, doughy and flabby; the amount of fat around the muscle fibers is in most cases excessive; slight changes in the diaphragm have been found by Councilman and Foot; the most conspicuous finding is the disproportion in the size of the fibers; the small fibers predominate in the majority of cases; some fibers are composed of 1 or 2 fibrils, others are of normal size. In certain cases large hypertrophied fibers were found (Archangelsky, Baudouin, Collier and Holmes, Concetti, Griffith, Kaumheimer, Lereboullet, Marburg, Mettenheimer, Reyher and Helmholtz); in a few the hypertrophy is only apparent on account of the presence of the very small fibers.

The cross striations are usually well preserved; they were indistinct or absent in the following cases: Mensi, Griffith, Kaumheimer, Lereboullet, Reyher, Skoog and Spiller. The sarcolemma nuclei are increased in number; in many undoubtedly this increase is due to an apparent disproportion in size of fibers and nuclei (fibers are small and nuclei are of normal size).

The amount of perimuscular fat is usually increased, as is also the connective tissue; in the following cases no increase was noted: Archangelsky and DeVilla.

No hypertrophic fibers were found in cases of Councilman, De Villa, Mensi, Bing, Rothmann, Skoog (Table 2).

PERIPHERAL NERVES

The peripheral nerves show deficient myelinization of their fibers, and increase of connective tissue. In certain cases the nerves appear small; in many, the nerve endings could not be demonstrated in the muscles. Empty neurilemma were found by Archangelsky, though all signs of degeneration were lacking; in the case of Griffith, the nerves were very much degenerated; the intramuscular fibers showed considerable degeneration and the medullary substance was broken down into small balls. Kaumheimer also found signs of severe degeneration in the nerves; the number of fibers was diminished, but no axis cylinder was found without a medullary sheath; the number of the nuclei of Schwann was increased; Marburg also found signs of degeneration

TABLE 2.—SUMMARY OF MUSCLE FINDINGS

	Normal Fibers	Small Fibers	Hypertrophied Fibers	Fat Increased	Connective Tissue Increased	Nuclei Increased	Transverse Striations Preserved	Longitudinal Striations Preserved
Archangelsky	++	+++	+	—	—	—	+	+
Baudouin	+	+++	++	+	+	+	+	+
Bing	+++	.....	.....	.....	.....	+ ?		
Collier	+	+++	++	++	++	++	+	+
Collier	+	+++	++	+++	+++	+++	+	+
Councilman	++	++	.....	.....	++	++	+	+
DeVilla	+	+++	.....	—	—	—	+	+
Concetti	+	+++	+	.....	—	—	+	+
Foot	+	+++	..	..	+	+	+	+
Griffith	+	+++	+	+++	+++	+++	+	—
Kaumheimer	.....	++	++	.....	++	++	+	—
Lereboullet	+	++	++	.....	++	.....	—	+
Marburg	++	+++	+	++	++	++	+	+
Marburg	+++	.....	+	++				
Mettenheimer	. ....	++	++					
Reyher	+	+	+	+	+	+	—	+
Rothmann	++	++	.....	+	+	+		
Skoog	+	+++	.....	++	++	++	—	+
Skoog	+	+++	.....	++	++	++		
Spiller	++	+++	.....	++	++	++	+	—
Mensi	.....	+++	.....	.....	.....	.....	—	—
Openshaw	+	+++	... ..	.....	.....	....	—	

and sclerosis; there were fewer fibers than normal, and those present were deficient in myelin; in many the entrance of nerves into muscle fibers can be seen, but the end plates cannot be demonstrated; the nerves in the case of Strauch showed marked, but not very profound degenerative changes; myelin sheaths were well preserved, but here and there it was thinned out; occasional breaks in the myelin sheath were present; the interstitial connective tissue was increased. Spiller and Lereboullet found nerves normal.

BLOOD VESSELS

The blood vessels were thickened in a number of cases (Skoog, Rothmann, Griffith, Marburg, Collier). The thickening is due to an increase of connective tissue.

OTHER FINDINGS

Small round cell infiltration was noted by Rothmann, Marburg, Collier and Holmes, and by Foot. The significance of these cells is hard to estimate; a few have looked on them as evidence of inflammatory changes. Rigor mortis was absent in all cases.

SUMMARY

To summarize, we may say that in the seven cases we may find pathologic changes in all the skeletal muscles and in the whole cerebrospinal system (from the brain to the end plates); the severity of the disease depends on the extent of muscular involvement and date of onset of disease; the more general is the distribution of muscular involvement, and the earlier the symptoms became manifest, the greater are the pathologic changes in the nervous system.

Pathologic changes have been found in the cerebrum, cerebellum, cord, peripheral nerves and muscles. The changes in the cerebrum consist in a diminution of the number of motor cells of the cortex and the cranial nuclei; the cord may be diminished in caliber; the motor cells of the ventral horns are reduced in number, and those present are of irregular shape and of smaller size; the anterior horns and roots are smaller than normal; the muscles are partially replaced by fat, and contain a considerable amount of connective tissue; some muscle fibers are normal; most are very small; many are hypertrophic; striations are well preserved in most cases; the sarcolemma nuclei are apparently increased in number; the peripheral nerves are reduced in size, contain fewer fibers and the fibers show deficient myelinization; the end plates can be demonstrated in only few cases; marked thickening of the adventitia of the blood vessels of the cerebrospinal axis was noted in a few cases (periarteritis); in a few cases changes (sclerosis) were noted in the thymus and the thyroid.

The presence of certain contractures, convulsions, athetosis and exaggerated reflexes point in certain cases to the involvement of the corticospinal tract.

PATHOGENESIS

Oppenheim believed this disease is due to an arrested development of the muscle tissue, but he did not exclude the possibility that the primary seat of the disease may be in the anterior horn cells.

Spiller also believed that this disease is due to an arrested development of the muscular tissue. Allen Smith, on the strength of finding a much sclerosed thymus in Spiller's case, believed that the whole clinical picture is due to the thymic changes.

Baudouin believed that arrested development alone could not explain all the pathologic findings in these cases; thus the proliferation of connective tissue, the enormous hypertrophy of certain fibers, the multiplication of nuclei of the sarcoplasm signify more than simple

arrest. He believes that dysfunction of the thyroid is the exciting cause that brings about this condition. Berti also expressed the view that this disease has something in common with myxedema. Concetti, above others, is of the opinion that the organs of internal secretion (especially the thyroid) are important etiologic factors in the production of this disease; he frequently observed improvement in these cases from the administration of thyroid extract; the underlying cause, however, he thought was to be explained by the assumption of abiotrophy of the whole neuromuscular apparatus. (Skoog was also of the same opinion.)

Marburg, on the strength of the necropsy findings in his case, did not believe that the disease is due to an arrested development. The findings in his case led him to the belief that he was dealing with a terminal process which had its inception in fetal life; the pathologic lesions in his case did not resemble those found in fetal life (arrested development), nor those seen in spinal (progressive) atrophy. It appeared to him that the process in his case was one of inflammation with small round cell infiltration, such as was noted by Rothmann in the nucleus of the hypoglossal nerve; he was, therefore, inclined to the conclusion that the disease was due to an acute fetal poliomyelitis.

Baudouin believed that the primary seat of this disease is in the cord; he believed that arrested development of the gray matter of the cord and the nerves precedes secondary atrophy of the muscles.

Bernhardt adduced some evidence to show that this disease may be due to a multiple polyneuritis.

Rothmann and others (Beevor and Wimmer), from a study of the pathologic lesions in their cases, believed amyotonia congenita to be a subgroup of Werdnig-Hoffman's type of paralysis. Bing, on the contrary, thought that the disease is due to an arrested development of the spinocerebellar tracts. Kaumheimer was of the opinion that this disease is due to a toxemia of unknown origin, or that it is of endogenous origin.

To us it appears that the pathogenesis of this disease is to be sought in a primary abiotrophy of the musculature and a secondary failure of proper development of the whole nervous system (cerebrospinal axis and peripheral nerves) brought about by deficient natural stimulation to its growth by the abiotrophic musculature.

When the heart is stilled life ends almost instantly. Besides this general life, the termination of which involves that of every part of the body, many of these parts have their own vitality; some of them may slowly die, while the life of all the rest goes on without impairment; when the failure is early, it is often due to a defect in vitality, a defect which seems to be inherent, the tendency thereto is born; to this degeneration or decay, in consequence of a defect of vital endurance, Gowers has applied the term "abiotrophy."

TABLE 3.—Summary of Pathologic Findings

Author	Cerebrum, Cerebellum, Medulla, Pons	Spinal Cord	Muscles	Peripheral Nerves
Archangelsky and Abrikosoff 7 months	Normal	Anterior roots small; posterior normal; complete absence of large ganglion cells of anterior horns and of Clark's columns; nerve fibers in cord diminished in number and lacking myelin; in the lateral anterior horns, myelinization incomplete and empty neurilemma	Muscles are thin, pale, flabby; no increase of nuclei; no increase of connective tissue; no increase of fat; fibers small, few, hypertrophied; striations distinct.	Nerve endings could not be demonstrated; all nerve cells appeared small; neurilemma empty; all degenerative signs lacking; many fibers not myelinated
2. Baudouin 4 months	Cells of 6th and 12th nerves were in a state of chromatolysis	At level of 8th cervical segment anterior horns were diminished in volume; no evidence of neuron phagocytosis; anterior nerve roots small; sheaths widely spaced; myelinization delayed	Connective tissue sheaths numerous and thickened; masses of small fibers; also very large fibers; nuclei increased in number; striations normal; no degeneration.	No fragmentation of the myelin; number of nerves not yet myelinated
3. Brunard	Doubtful case; no macroscopic lesions found	.....	Nothing said about muscles, except a little sclerosed.	Histologic study promised but not reported; nothing abnormal found macroscopically
4. Collier and Holmes 7 years	Nuclei of hypoglossal and ambiguus nerves showed pathologic changes	Unmistakable pathologic changes in the ventral horns; the large cells were reduced in number; those present small; Clark's column normal; anterior roots very slender	Remarkably pale; infiltrated by fat; few normal fibers; most prominent change in extreme smallness of fibers; proliferation of sarcolemmia nuclei; many enormous fibers present; increase of connective and fat tissue; blood vessels thickened; striations very distinct.	Nerve fibers rather far apart; myelin sheaths rather poorly developed; roots slender
5. Collier and Holmes (dropsy)	.....	.....	Macroscopically, pale and very much infiltrated with fat; many fibers were extremely small; striation well preserved; marked proliferation of nuclei; enormous fibers present; connective tissue greatly increased; notable amount of loose fat tissue	.....
6. Councilman and Dun, 7½ months	Normal	Slight degeneration in the myelin of the posterior columns; also in anterior and posterior nerve roots and in spinal ganglia; sections of the cord showed very slight evidence of change; no diminution in the number of cells in the anterior columns; neuroglia normal	Muscles thin, color and consistency normal; infiltrated with fat; normal fibers and very small muscle fibers; nuclei increased? connective tissue increased; striations normal in most fibers; no fatty degeneration; diaphragm slightly involved	No change in the nerves; number of nerves in the muscles was diminished; nerves in the muscle tissue were found, which showed evident degeneration; a few peripheral nerves lacked myelin; no nerve endings were found in the affected muscles
7. DeVilla	.....	Deficiency in the number of anterior horn cells; slight rarefaction of pyramidal bundles; a few fibers without sheaths	Muscles pale; fibers small; no increase of nuclei; no increase of connective or fat tissue.	.....
8. Foot, 3½ months	Changes in the formatio reticularis and substantia reticularis	Anterior horns were the seat of pathologic lesion; cells were reduced in number and size; some showed vacuolar degeneration and acute swelling; horns shrunken in size; white matter pale, except columns of Goll and Burdock; many small cells resembling the posterior horn cells were present; marked gliosis in anterior horns	Marked differences in size of muscle fibers; most very slender; fat and connective tissue increased; nuclei of normal appearance; muscle pale like "raw pork"; diaphragm slightly involved; striations preserved; fatty changes in some fibers, and others were hyaloid	Marked decrease in medullary sheaths; smaller muscle fibers seemed to be without innervation

TABLE 3.—SUMMARY OF PATHOLOGIC FINDINGS—(*Continued*)

Author	Cerebrum, Cerebellum, Medulla, Pons	Spinal Cord	Muscles	Peripheral Nerves
9. Griffith, 25 months	Brain unusualy large; cells of hypoglossal nucleus diminished in number; pia edematous	Spinal cord membranes edematous; anterior roots small; cells in the anterior horns much diminished in number; Clark's column not affected; anterior roots much degenerated	Great atrophy of fibers; transverse striation preserved, but not longitudinal; atrophy not general; a few very large muscle fibers found; number of nuclei increased; connective tissue fat greatly increased; formation of fat within the muscle fibers was observed only in this case	Very much degenerated; intramuscular fibers showed considerable degeneration; medullary substance broken into small balls
10 Bing (biopsy)	.....	.....	Muscle was normal in all respects except perhaps there was an increase in the number of nuclei	.....
11. Kaumeimer	Increase of glia in cerebrum, medulla and cord; pathologic changes in cells of nuclei of ambiguus and hypoglossal nerves	Gliosis; pathologic changes in anterior horn cells and in cells of Clark's column; slight signs of degeneration in the anterior nerve roots; anterior roots small; cells of anterior horns small, few, pyknotic, degenerated fibers in tracts but did not lack myelin	Manifold symptoms of degeneration; atrophic and hypertrophic fibers, vacuolation, nuclear increase and increase of connective tissue; transverse striations distinct, except in hypertrophic fibers	Signs of severe degeneration; number of fibers diminished, but no axis cylinders without medullary sheaths found; nuclei increased (Schwann)
12. Lereboullet and Baudouin, 15 months	Brain normal	Cord normal; no diminution in size or number of the cells in the anterior horns	Muscle lesions were marked; fibers were of irregular size; transverse striations absent; longitudinal present; nuclei increased; some fibers small; some very large; connective tissue increased	.....
13. Marburg, 3 months	.....	Posterior roots normal; axonal degeneration only in isolated instances; increase in glia nuclei and fibers; increased number of bloodvessels; degeneration of anterior horn cells; deficient myelinization; increase of connective tissue and glia in cord	In addition to normal fibers were found very thin fibers with many nuclei; a few hypertrophic fibers; fat and connective tissue was increased; transverse striation distinct, also longitudinal; nuclei apparently increased	Signs of degeneration and sclerosis; fewer fibers; these were deficient in myelin
14. Marburg (biopsy)	.....	.....	Occasional hypertrophic fibers found; fairly large amount of fat near normal muscle fibers; no atrophic fibers found	.....
15. Mettenheimer	.....	Recent disease of ganglion cells, atrophy and absence of anterior horn cells	Muscle fibers were atrophic and others were hypertrophic	.....
16. Mettenheimer	.....	Severe degenerative signs in the anterior horn cells of the entire cord	.....	.....
17. Reyher and Helmholtz (biopsy)	.....	.....	In proximity to normal muscle fibers are found either little or much altered fibers, transverse striation lacking; difference in diameters of muscle fibers was especially marked; nuclei interstitial connective tissue and fat increased	.....
18. Pollock	Necropsy performed but not reported	Thymus enlarged; thyroid large	.....	.....

TABLE 3.—Summary of Pathologic Findings—(*Continued*)

Author	Cerebrum, Cerebellum, Medulla, Pons	Spinal Cord	Muscles	Peripheral Nerves
19. Rothmann	At nucleus of glossopharyngeal marked development of blood vessels; cells were degenerated and there was a diminished number of motor cells in the nuclei; same was true of vagus nucleus. In the height of the pyramidal tract there was still more marked absence of the motor ganglion cells; also in nucleus of hypoglossus; cerebellum small	Development of fine fibers was much diminished, many capillaries were present; almost complete absence of anterior (ganglion) horn cells and of Clark's columns; posterior horns normal; anterior roots small; many fibers lacked sheaths; posterior roots normal except in lumbar region (small); glia increased	Interstitial connective tissue increased; nuclei increased; increased fat between muscle fibers; muscle fibers, some gone; others replaced by small round cells; normal fibers also present; muscles pale	Nerves themselves were small; axis cylinders were small; connective tissue increased and the nuclei were numerous; incomplete myelinization; entrance of nerves into muscle fibers could be seen, but endplates were absent
20 and 21. Skoog (biopsy) 2 cases	.....	.....	Not one muscle bundle appeared normal; were very small; no hypertrophic fibers present; transverse striation gone; connective tissue and fat increased, especially between muscle bundles; nuclei increased	.....
22. Skoog (biopsy)	.....	.....	Muscle pale and contained much fat; muscle bundles could be seen terminating abruptly in a replacing adipose tissue; much fat between bundles; no hypertrophic fibers; nuclei increased; blood vessels greatly thickened	.....
23. Spiller 22 months	Normal (paracentral lobules small; Betz' cells few in number)	Normal	Increase in nuclei of connective tissue; muscle fibers were small; unusually large muscle fibers were not observed; transverse striations were well preserved; longitudinal were not so distinct; muscles have a hyaloid appearance; large amount of fatty connective tissue and increase in the nuclei of the connective tissue	Normal. Nerve fibers within the muscles from the sole of the foot appeared to be normal
24. Strauch (partial necropsy)	.....	.....	Muscles showed marked condition of atrophy; individual bundles were small and separated from each other by a large amount of fat; striations gone; fibers were narrow and varied in size; no hypertrophic fibers were present; nuclei increased, with karyokinetic figures	Marked but not very profound degenerative changes; myelin sheaths were well preserved; here and there it was thinned out; occasional breaks in the myelin sheath were present; the interstitial connective tissue was very much increased
25. Berghinz	Nerve cells of cerebellum small; hypoplasia and microgyria of cerebrum	Cells of anterior horns small and few	.....	.....
26-30. Mensi (5 cases)	.....	Anterior horn cells reduced in number and are multipolar; large ganglion cells absent	Muscle fibers and bundles slender; cross striations absent or indistinct	No nerve endings could be found
31. Concetti 53 days	Cerebellum and Purkinje's cells were few and altered in shape; all layers of cerebrum reduced in volume; glia normal	Anterior roots smaller than normal; anterior horn cells few and small; large ganglion cells absent; Clark's columns normal; no changes in the glia; blood vessels and the meninges	Muscle fibers very small and some larger; some hypertrophic; striations normal; nuclei increased; no increase in interstitial connective tissue; no increase of nuclei; no sclerosis	A few fibers lacked myelin, but no degeneration was present
32. Openshaw 7½ years	.....	.....	Transverse striations absent fatty infiltration and signs of regeneration	.....

We may perceive an illustration of the failure of the life of the hair follicles of the scalp, which must be the essential cause of early baldness; premature grayness is another example of early death. In the various forms of idiopathic muscular atrophy, we have true examples of abiosis; in these the muscular fibers, after full development, cease to maintain their own nutrition; they slowly waste and a large number of them ultimately perish. It is a defect of vital endurance, truly congenital, in so far as the tendency is concerned. We have further proof of its dependence on a congenital tendency in its occurrence in several members of the same family, chiefly in the males, the girls who do not suffer conveying the morbid tendency to their sons.

The neurons depend for vitality on the cell from which the fibers proceed; the groups of neurons which are differentiated in function differ also in their tendency to decay and in their degree of vitality. These neurons differ not only in the lapse of life, but also in the early stage; some are structurally complete sooner than others and thus are distinguished in the beginning of life as well as in its ending.

Whenever the nerve elements waste there is an overgrowth of the interstitial neuroglia, the connecting and supporting tissue which lies between them. The neuroglia is a residue of the embryonal tissue from which the nerve elements also develop. When there is local arrest of development of the latter, the embryonal tissue persists in tracts adjacent; the two elements, the neural and the neurologic, seem to have a common but inverse vitality; it is in consequence of this that the interstitial tissue overgrows when the nerve elements decay, and may be at first more conspicuous.

Assuming that the paresis of the musculature in this disease is due to an early abiotrophy, how can we explain the changes in the nervous system? It appears to us that a knowledge of the development of the nervous system may throw some light on this subject.

The nervous organs of the higher animals, including man, consist of enormously intricate systems of interwoven nerve cells or neurons. These neurons possess a nucleated cell body from which extremely attenuated processes, the nerve fibers, reach out to the most distant parts of the animal. These processes are the most characteristic parts of the neuron. The neurons are highly specialized in structure and exhibit profound physiologic differentiation; functional specialization among these elements has come to be so extreme that the nervous system may be described as one in which differentiation has reached to its very cells.

The neurons may be classified: (1) the afferent (sensory neuron) extending in general from the surface of the animal to the central organs and transmitting sensory impulses. (2) The efferent neurons connecting the central organs with the muscles, etc., and transmitting

efferent impulses, and finally (3) the association neurons which lie entirely within the central organ and connect one part of this organ with another (the association neurons far outnumber those of the other two classes and constitute the chief mass of these organs).

Almost all nervous operations in higher animals involve all three classes of neurons. The typical nervous reactions of these animals consist of a sensory stimulation followed by a motor response; this operation has been called a reflex. The ordinary reflex may be said to involve, in sequence, the activity of a receptor (sense organ), adjustor (central organs) and an effector (not neurons, but muscle fibers or gland cells). Our own reflexes are sometimes associated with consciousness and sometimes not.

From a study of the neuromuscular mechanism (which has no adjustors) of the sea anemone, we are bound to conclude that the central nervous organs (adjustors) were evolved only after the appearance of sense organs and muscle.

In studying the reactions of one of our common sponges (Stylotella), Parker was impressed with the extreme slowness with which the animal responded to a stimulus; transmission in the stylotella, resembles very closely the kind of transmission seen in ciliated epithelium. This probably represents a primitive form of protoplasmic transmission, a forerunner of the true nervous impulse. Sponges probably possess no true nervous tissue; their muscles are brought into action almost entirely by the direct effect of the stimulus, rather than through nerves, and this accounts for the slow response to external disturbances. The state of the sponges suggests that nerve and muscle have not been differentiated simultaneously, but that muscle preceded nerve in its evolution and that sponges represent animals with effectors, but without differentiated receptors. If it may be asserted that the sense organ preceded the central nervous organ, it may also be maintained that muscles preceded sense organs. Thus the three elements of the reflex arc of higher animals were probably evolved separately and in the order of effector, receptor and adjustor. This is proved by certain muscles of man. The sphincter of the iris, in lower vertebrates (though under influence of nerves) was shown by Stemace to be directly stimulated by light; also the embryonic vertebrate heart, which beats before it has become invaded by nerves.

It seems, therefore, that muscle arose first, and the simple effectors thus produced were the first elements of the neuromuscular mechanism. These effectors were directly stimulated and consequently slow in action. They afforded tissue around which nervous tissue first differentiated in the form of sense organs or receptors, whose function it was to serve as triggers to initiate muscle action quickly. As these receptors became more highly developed, a third element, the central

nervous organ, arose from the nervous element between the receptor and the effector. This organ, the adjustor, served as a means of conducting and modifying the sensory impulses on their way from the receptor to the effector, and ultimately it served as a storehouse for the nervous experience of the individual, as the seat of his intellectual life.

There is sufficient evidence at hand to show that Nissl degeneration, followed by gradual atrophy and disappearance, occurs when neurons are deprived of their function by any cause, as the removal of a limb.

It is reasonable to suppose (in view of the dependence of proper neural development on proper muscular development) that the more extensive and intensive is the pathologic condition of the musculature and the earlier it develops, the more extensive and intensive will the pathologic process be in the nervous system; data derived from necropsies on cases of amyotonia congenita substantiate this assumption.

In accordance with this hypothesis, many clinical findings, which could not previously be correlated with the necropsy findings, seem to find a rational explanation.

From what has been said, we would expect but little involvement of the nervous system in cases in which the onset of the disease was delayed for a number of months after birth, and in cases in which the muscle was but slightly affected; on the contrary, the earlier in fetal life and after birth the muscles become affected, and the more severe the process, the more severe will the pathologic process be in the nervous system.

To summarize: We believe that amyotonia congenita is primarily a muscular disease, a disease which is due to an inborn, inherent defect in the vitality of the musculature; and as proper neural development depends on proper muscle development, the earlier, the more intensively and the more extensively the musculature becomes involved in this abiotrophy, the earlier, the more intensively and extensively will the nervous system become involved.

CLASSIFICATION OF MYOTONIA CONGENITA

There is no group of diseases which offers such difficulties in its classification as do the progressive muscular atrophies; various classifications have been suggested, but not one is sufficiently comprehensive to include all known forms, nor sufficiently differentiated to exclude varieties which pathologically do not belong to the group.

Clinicians for many centuries have described progressive muscular wasting. Pictures and images in stone and wood of the muscular atrophies and muscular dystrophies dating from the fifteenth, sixteenth

and seventeenth centuries are in existence. Van Sweeten, Abercrombie and others gave general descriptions. This group was first broken into by Duchenne, in 1849, by the loose description of a special type, which a year later Aran supplemented. Cruveilhier, in 1853, and Luys, in 1860, sharpened the picture somewhat by their demonstration of the exclusive implication of the anterior horns. In 1853, Duchenne set aside the pseudohypertrophies, the muscular features and varieties of which were later demonstrated by Eulenberg (1866), Charcot, Leyden and Dejerine. Thus it took thirty years for the sorting out of this medley of muscular atrophies.

The very large and extremely motley group of muscular dystrophies has also been built up of a variety of forms since Duchenne, in 1849, first described the fatty pseudohypertrophies, and later, in 1868, spoke of them as myoscleroses. Leyden (1876) and Möbius (1879) described certain hereditary forms, while Erb, in 1883, first brought some order into the confusion of the atrophies and dystrophies by showing that in certain forms the lesion was predominantly muscular and not nervous. The myopathies make a fairly consistent group, although the forms may not resemble one another clinically at different periods of their development, yet they have a number of common factors.

In 1891, Werdnig described a new form of spinal progressive muscular atrophy in two sisters. Hoffman substantiated the findings of Werdnig and reported twenty cases in three families, all afflicted with the same disease. This disease has since become known as the Werdnig-Hoffman type of spinal progressive muscle atrophy of children; and finally, in 1900, Oppenheim described a syndrome which he thought could be differentiated from all previously described varieties; future observations proved the correctness of his investigations and the disease is now known as Oppenheim's disease, or "amyotonia congenita."

The spinal motor neuron is differentiated into three structures: the anterior horn cell, the motor nerve fiber and the muscle plate; if a clinical division could be made in strict accordance with the pathologic alterations of these structures, great advance toward the simplification of the classification of this group of diseases would be made.

The classification of Kügelgen seems to be the best:

A. Muscular dystrophies (myopathies)
   - I. Pseudohypertrophic (Duchenne)
   - II. Juvenile type (Erb)
   - III. Facioscapulohumeral (Landouzy, Dejerine)
   - IV. Distal type (Gowers)
   - V. Myotonia atrophica
   - VI. Mixed and transitional types

B. Amyotonia congenita

TABLE 4.—Differential Diagnosis

	Muscular Dystrophy	Werding-Hoffman Type	Oppenheim's Disease
Heredity	Usually hereditary and familial	Hereditary and familial	Not hereditary; rarely familial
Onset	Gradual during childhood; rarely in infancy (2 to 7 years), after learning to walk.	Gradual, usually in the second half of first year; born healthy; usually before walking was accomplished	Congenital or in the first few months of life; suddenly, following acute ailment
Muscles affected	Pectoralis major, rhomboidei, serratus anterior most often the seat of early atrophy; bulbar muscles hardly ever affected.	Muscles of pelvic girdle and muscles of small of back first to be affected; later muscles of back, shoulders, thighs, arms; bulbar muscles rarely affected	Muscles of legs most frequently involved; less marked involvement of arms, back, neck; bulbar muscles not infrequently affected (face)
Atrophy	Present and visible in some muscles; pseudo-hypertrophy visible in other muscles	Atrophy present and visible; no hypertrophic muscles observed	Atrophy not present; if present not visible; no hypertrophic muscles observed
Tendon reflexes	Disappeared gradually; the Achilles is apt to persist or be increased, with hypertrophy not observed	Absent; never returned after disappearance	Absent or feeble; returned with improvement in muscle power
Fibrillary twitchings	.....	Twitching and tremors sometimes seen	Not observed
Electrical reactions	Quantitative diminution to total absence	Reaction of degeneration	Quantitative diminution to total absence
Course	Gradual deterioration	More rapid deterioration; usually died in childhood	Gradual improvement; never complete recovery
Pathology:			
Brain	Normal; head in a few cases asymmetrical; parietal and temporal bones prominent; prognathism; mental deficiency, idiocy, epilepsy not infrequently observed	Mentality usually normal; no pathologic lesions found in the brain	Mentality usually normal; backwardness in a small percentage; usually normal; rarely showed atrophy; absence of cells in motor nuclei
Spinal cord	Normal	Absence of anterior horn ganglion cells in the whole cord up to medulla; the cells showed swelling, atrophy, diminution of chromatophile substance and eccentric position of nuclei; myelin sheaths showed degenerative changes; slight changes in tract of Goll and pyramidal tracts; marked degeneration of anterior horns	The motor cells of anterior horns were reduced in number; anterior horns and roots were small; degenerative signs were few; inflammatory signs were lacking
Peripheral nerves	Normal	Marked signs of degeneration	Reduced in size; showed deficient myelization; endplates visible in only few cases
Muscles	Simple atrophy and hypertrophy of muscle fibers; pseudohypertrophy of muscles due to infiltration with fat; fat increased; connective tissue increased; muscle fibers showed splitting, division and vacuolation; nuclei increased; hypertrophic fibers lost their polygonal shape; transverse striation was obscure	Simple atrophy; more or less fat deposition between the muscle bundles; muscles "enminiature"; no increase of nuclei; fatty or amyloid degeneration of muscle fibers; rarely hypertrophic fibers seen	Most muscle fibers were small; many were hypertrophic; intermuscular fat and connective tissue increased; striations well preserved; nuclei apparently increased
Contractures	Pes equinus; deformities of elbows, knees, hands and feet; short hands and short feet	Mostly of fingers and toes in form of claw deformities and equinovarus; deformities of back	Contractures of arms more frequent than in other forms; pes equinus; deformities of back (postural)

C. Progressive nuclear atrophies (myelopathies)
  I. a. Chronic anterior poliomyelitis
     b. Aran-Duchenne's disease
     c. Werdnig-Hoffman type
  II. Bulbo-pontive types (Möbius-Heubner)
  III. Pontomesencephalic forms

D. Spinal neuritic atrophies
  I. Charcot-Marie-Tooth type
  II. Tabetic type (Dejerine-Sottas)
  III. Peroneal-arm type (Sainton-Haevel)

The two diseases from which amyotonia congenita is to be differentiated are from the spinal progressive muscular atrophy (type Werdnig-Hoffman) and from the pseudohypertrophic form of muscular dystrophies (type Duchenne). In some respects it simulates both; in many it differs considerably. The differential points are noted in Table 4.

Although the main points have been stated in the differential diagnosis, these three diseases are not so sharply defined as it would appear. Thus at times, in true cases of muscular dystrophy, there is found a true reaction of degeneration; a few observers have also noted fibrillary twitchings in muscular dystrophies. The presence of mental deficiency, idiocy, and epilepsy can hardly be explained in the strength of pure coincidence; they occur too often; at times, in true cases, the anterior horn cells were also involved (Clarke, Heubner, Peck, Erb, Schultze, Singer).

Improvement is the characteristic symptom of amyotonia congenita, yet in many cases there was progressive deterioration without ever showing any amelioration; on the contrary, progressive deterioration is characteristic of myopathies, and yet a few isolated cases have shown complete arrest of symptoms (Mariana). Return of knee jerks which is most usually found in amyotonia congenita, has also been observed in the dystrophies (Jendrassix).

From a study of all the cases reported and from the facts mentioned we are inclined to group amyotonia with the myopathies and not with the myelopathies; amyotonia congenita seems to be a connecting link between muscular dystrophies, on one hand, and spinal progressive muscular atrophies, on the other.

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DIAGNOSTIC SIGNS FROM THE SCALENI, INTERCOSTAL MUSCLES AND THE DIAPHRAGM IN LUNG VENTILATION *

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During the past few years, respiration has come in for a bountiful share of physiologic and clinical research, but all of the research has been directed toward gaining some understanding of the exquisitely nicely balanced relations of excitatory and inhibitory influences which modify the rate, rhythm and amplitude of respiration.

Chemistry of the blood in its relation to respiratory function has also been the subject of much research, but the simpler problem of lung ventilation and its clinical analysis has been neglected. In every clinical examination we should form some definite idea about the volume, density and extensibility of the upper and lower lobes of the lungs. An understanding of these three physical attributes is the goal toward which most methods of physical examination of the lungs have been directed. Density of the lung, with some adventitious signs, has occupied the attention of clinicians much more than volume and extensibility of the lung.

To form a clear estimate of volume and extensibility of the lung we must have a clear conception of the physiologic mechanism by which lung ventilation is accomplished. In every case we must estimate:

1. The inspiratory enlargement of the thoracic cage in three dimensions.

2. The relative height of that portion of the diaphragm underlying the heart, and the height of the two leaves of the diaphragm underlying the lung.

3. The share of the scaleni in the movement of the upper four ribs.

4. The share of the intercostal muscles in the movements of all the ribs from the second rib to the twelfth.

5. Beside the above named diagnostic points, we must also differentiate the evidences of diaphragmatic activation from the evidences of diaphragmatic excursion.

In other words, to have a clear conception of the ventilatory function of the lung we must in every case point out the evidences of the functions of the scaleni, the intercostal muscles and the diaphragm.

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* From the Medical Department of Lakeside Hospital.

Briefly stated, the function of the scaleni muscles is solely to form a point of fixation in the first rib from which the second, third and fourth ribs are elevated. The increase of the anteroposterior and transverse diameters of the thorax is accomplished entirely by the intercostal muscles. The increase of the longitudinal diameter of the thorax is due solely to the descent of the diaphragm. These are the simpler facts, but the diagnostic problems which arise in clinical work require us to recognize what modifications of the respiratory excursion of the thorax betray a paralysis of the scaleni muscles, or paralysis of the intercostal muscles, or paralysis of the diaphragm.

We must also differentiate between evidences of activation of the diaphragm and evidences of excursion of the diaphragm.

I shall also show how we can recognize moderate depression of the middle portion of the central tendon of the diaphragm, as occurs in enlargement of the right ventricle of the heart and with small amounts of fluid in the pericardial sac. We can also recognize a depression of the left lateral portion of the central tendon due to enlargement of the left ventricle when the right ventricle is not enlarged.

By studying the inspiratory excursions of the costal margins we can recognize various degrees of depression of the muscular leaves of the diaphragm, namely: (a) when the under surface of the leaf is convex, as in very large pleural effusions; (b) when the leaf approximates a plane, as in moderate effusions; and (c) when the convexity of the upper surface of the leaf is increased, as occurs in hepatic enlargement and accumulations of pus or fluid between the diaphragm and liver. This can be learned by studying the inspiratory excursion of the median and lateral portions of the costal margins. This is all possible because the movement of the costal margins expresses accurately the balance between the intercostal muscles and diaphragm in their contest for mastery of the costal margins.

The median portions of the diaphragm are much less arched than the lateral portions, consequently much less depression of the median portion of the diaphragm is necessary to modify the normal excursion of the internal portion of the costal borders than is required to modify the normal excursion of the external portion of the costal borders.

With this general statement of the argument I shall proceed to illustrate the specific points by a number of clinical and experimental data.

Ventilation of the Upper Lobes of the Lungs.—Long ago the observation was made that the infraclavicular region exhibited an "undulatory movement during inspiration." This undulatory movement is due to the varying size of the upper five ribs. The lengths of the upper five ribs increase from the first to the fifth.

During inspiration the first rib is not elevated, but the second, third, fourth and fifth ribs are elevated by the so-called bucket handle move-

ment. The maximum movement of a rib will be in that portion farthest from the axis of rotation, consequently the external portion of the rib will move through a greater distance than the parts nearer the axis of rotation.

The distance through which a rib will move in response to an inspiratory activation of the intercostal muscles will be limited by the extensibility of the underlying lung. The movements of the upper five ribs faithfully mirror the movement of the underlying lung, consequently any disease which will impair the extensibility of the lung will modify the normal undulatory movement of the upper five ribs.

Any disease of the pleura, occlusion of a bronchus, or inflammatory process in a lung will diminish its extensibility. Extensibility is the first attribute which is modified in any inflammation of the lung. This diminution of extensibility can be detected before any increase of density is demonstrable. Consequently, the sign bears a very important significance in the early recognition of pulmonary tuberculosis of the upper lobes.

The undulatory movement varies in different normal persons just as the pitch of the percussion note varies. The more flexible the cartilage of the ribs the more active the bucket handle movement will be.

This phenomenon is observed best by the examiner when standing at the right of the recumbent patient. The examiner should use his left hand. Place the tip of the ring finger on the second rib at the midclavicular line, the tip of the middle finger on the third rib midway between the midclavicular and the anterior axillary line, and the tip of the index finger on the fourth rib in the anterior axillary line. The patient is then instructed to make a moderately rapid and moderately deep inspiratory movement. The finger on the third rib will be observed to move further than the finger on the second rib and the finger on the fourth rib will move further than the finger on the third rib. The movement in each rib from above downwards succeeds and exceeds that in the rib just above.

Should there be only a moderate impairment or diminution of ventilation in the upper lobe the three ribs will move in unison and move the same distance, so the undulatory phenomenon will be lost although all the ribs involved may exhibit a considerable excursion during inspiration. By comparing the undulatory movement on the two sides we have a very delicate method of comparing the amount of ventilation in the upper portions of the upper lobes.

Anything which will slightly diminish the amount of ventilation on one side or the other will cause a disparity in the undulatory movement between the two sides. We find this true in any disease which will encroach on the air spaces, or invade the interstitial tissue of the lung or occlude a bronchus or displace a part of the lung as occurs in

mediastinal tumor. The undulatory movement will be diminished on the left side when the heart is enlarged in an upward direction or when the pericardial sac is distended and also when the pleura is thickened so its extensibility is diminished.

Localized emphysema of an upper lobe of the lung will reveal a diminished undulatory movement because the ribs are in a partial inspiratory phase at the beginning of an inspiration.

If the sign is taken for exactly what it amounts to, namely, a diminished ventilatory volume of the upper part of the upper lobe, it will be of great diagnostic service. Further diagnostic signs must aid in determining what has contributed to a localized diminution of ventilatory function of the lung.

The greatest practical use of this sign rests on the fact that in all diseases of the lung a diminution of extensibility is demonstrable earlier than changes in volume or density of the lung can be demonstrated. Certainly in the early or latent periods of pulmonary tuberculosis, diminished extensibility can be demonstrated when no evidences of alteration in density or volume of the lung can be elicited, and also when all adventitious signs are absent.

An exact study of the comparative extensibility of the upper lobes should constitute a part of routine clinical examinations. In our experience at Lakeside Hospital, this procedure has been the source of many diagnostic successes, and it has also aroused many interesting diagnostic problems which otherwise would have escaped our observation.

Rôle of the Scaleni Muscles.—The following case gave rise to a study of the differentiation between the rôle of the scaleni and intercostal muscles in respiratory excursion of the upper five ribs.

A child about 2 years old in the children's ward at Lakeside Hospital, was admitted with well advanced signs of a congenital muscular disease. There was absolute paralysis of all the muscles which contribute to movements of the head on the spine. The respiratory excursion of the thorax presented a very unusual picture. During inspiration the manubrium with the first three ribs were drawn strongly downward and inward; the fourth ribs remained stationary but the fifth ribs and those below moved upward to an unusual extent. The subcostal angle widened much more than in normal children. Both hypochondria moved outward much more than in normal cases. There was, however, no inspiratory retraction of the suprasternal notch or of the supraclavicular spaces.

The exaggerated spreading of the hypochondria and descent of the first three ribs and manubrium with each inspiration presented a very unusual and perplexing problem for analysis. The question which arose was whether the entire picture was due solely to paralysis of the scaleni muscles, or whether the upper intercostal muscles also shared in the progressive muscular disease.

EXPERIMENTS

Experiment 1.—Under ether anesthesia the three scaleni muscles of the right side of a dog were exposed and cut immediately above the first rib. The first, second and third ribs of the right side were drawn downward with each inspiration. The fourth rib remained stationary and the fifth rib, with all those below it, moved upward as in a normal animal. On the left side the first rib remained stationary but the second, third, fourth and fifth ribs exhibited the usual normal undulatory movement already described. When the scaleni of the left side were cut as those of the right side were cut in the beginning of the experiment, the same phenomena of respiratory excursion were produced on the left side. The respiratory excursion of the dog's thorax was identically like that of the child's thorax.

Experiment 2.—A young dog about 1½ years old was given morphin and ether anesthesia. The sternomastoid and scapula of the right side with all its muscular attachments were removed so there were only the scaleni, intercostal muscles and diaphragm left. The respiratory excursion of the entire thorax was unchanged. Then the scaleni were cut on the right side and the same changes in respiratory excursion were plainly seen on the right side as described in Experiment 1. The scaleni of the left side were then severed and the same descent of the upper three ribs with fixation of the fourth rib and upward movement of the fifth ribs with those below occurred as in the former experiment.

If the upper end of the sternum was grasped with forceps and held in position so the manubrium could not descend during an inspiratory movement, there was a return to the normal inspiratory evolution of the upper ribs. When the manubrium was released the picture of the child with paralysis of the scaleni was again reproduced.

Experiment 3.—Under morphin and ether anesthesia the spinal cord of a dog was severed at the sixth cervical segment. The scaleni and diaphragm were thus preserved, but all the intercostal muscles were paralyzed. There was no inspiratory descent of the upper ribs or manubrium, but with each inspiratory descent of the diaphragm the upper lateral portions of the thorax were retracted. There was no elevation of the first ribs during inspiration.

Experiment 4.—The following experiment shows how the structure of the bony thorax may greatly modify the phenomena thus far described. A well grown, young dog which still had its puppy teeth, was given morphin and ether anesthesia for the purpose of making other observations, but incidentally the scaleni muscles on both sides were exposed and severed. Instead of the phenomena observed in our former experiments, the first ribs were drawn downward with each inspiration, the second ribs were drawn in an upward direction, so that the second ribs actually overrode the first ribs to a slight degree. The manubrium was not drawn downward. The second, third and fourth ribs exhibited the normal undulatory movement seen under normal conditions.

COMMENT

These experiments suffice to show that the scaleni do not contribute to the inspiratory elevation of any of the ribs. The scaleni simply supply an anchorage for the first ribs only, and the evolution of the ribs during inspiration from the second downward is accomplished entirely by the intercostal muscles. I have had the opportunity of seeing only the one clinical case of paralysis of the scaleni, so from our experimental experience on dogs we may expect to find the inspira-

tory movements of the upper four ribs to differ in patients, just as occurred in our dogs.

There may be an inspiratory descent in a caudad direction of only the first ribs with a normal evolution of all the ribs from the second rib downward, or there may be an inspiratory descent of the upper three ribs and manubrium with fixation of the fourth rib and elevation of all the ribs below the fourth. This will depend on the mobility of the upper ribs and the manubrium. If the upper ribs and manubrium form a comparatively rigid structure, then only the first rib will be drawn downward with each inspiration if the scaleni are paralyzed; but if the manubrium and upper ribs are quite flexible, as in the child described, then paralysis of the scaleni will cause the inspiratory excursion of the thorax to present a striking picture of increased spreading of the hypochondria and retraction in a caudad direction of the manubrium and upper three ribs.

The Diaphragm and Intercostal Muscles. — The diaphragm and intercostal muscles are antagonists in two ways: The intercostals serve to increase the anteroposterior and transverse diameters of the thorax, and the diaphragm serves to increase the longitudinal diameter of the thorax. Activation of the intercostal muscles will tend to diminish the longitudinal diameter of the thorax unless resisted by the diaphragm, and activation with excursion of the diaphragm will cause a diminution in the other two dimensions of the thorax, with narrowing of the subcostal angle, unless resisted by the intercostal muscles. Much confusion has been introduced into this subject by failure to differentiate the evidences of diaphragmatic activation from the evidences of diaphragmatic excursion, and also the failure to recognize the significance of the arch of the diaphragm as a whole, and the significance of varying curves of different parts of the diaphragm has led to much confusion and misinterpretation of the respiratory movements of the costal margins.

The modern interpretation of the function of the intercostal muscles and the diaphragm has hitherto rested on the work of Duchenne[1] of Boulogne. A critical review of Duchenne's work is interesting in the light of more modern writers and the author's observations on patients and animals.

Duchenne proposed the following problems in his work:

Does the diaphragm in its contraction constrict the lower part of the thorax by drawing the lower ribs downward, or, on the contrary, does the diaphragm increase the transverse and anteroposterior diameters of the lower half of the thorax by lifting the diaphragmatic ribs upward and outward?

1. Duchenne: Recherches Electro-Physiologiques et Therapeutiques sur la Diaphragme, 1853.

Does there exist a difference between the physiologic action of the diaphragm in its relation with the abdominal viscera and the action of the diaphragm when it is deprived of its visceral relations?

Finally, what is the mechanism of the action of the diaphragm on the thoracic walls?

Then follows an interesting historical summary of the study of the diaphragm which shows what difficulty attended the interpretation of the function of the diaphragm in conjunction with the spread of the hypochondria and widening of the subcostal angle.

The anatomists of antiquity recognized only one muscle of inspiration and ascribed to the diaphragm the duty of carrying the ribs upward and outward. But Galen recognized other muscles of respiration and ascribed to the diaphragm only the function of lifting and spreading the lower ribs. Vesalius, however, questioned this. He interpreted the activation of the diaphragm as resulting in an elevation of the diaphragm. Columbus (his pupil) denied this and said the diaphragm was depressed by inspiration, but that the diaphragm was relaxed during inspiration. Activation of the diaphragm constricted the lower ribs but owing to relaxation during inspiration, the diaphragmatic ribs were permitted to spread.

Borelli, the physicist, cited by Duchenne, was the first to claim that the diaphragm contracted during inspiration and increased the longitudinal diameter of the thorax, and by virtue of its attachments to the ribs must necessarily by its action constrict the lower part of the thorax. Borelli asserted the diaphragm could not act independently of the intercostal muscles.

The idea of Galen was forgotten until 1833, when Magendie again took up the idea and said that the spreading of the lower thorax from diaphragmatic contraction and descent was due to the resistance of the viscera under the vault of the diaphragm, and as the ribs were readily moved, the compression of the viscera caused increase in the transverse diameter of the upper abdomen and thus pushed the ribs outward. Duchenne says Magendie never supported his idea, however, by any animal experiment.

In 1843 Beau and Maissiat undertook to establish the doctrine of Galen by experimental methods. They cut the lower six intercostal structures through from the sternum to the vertebrae on both sides after cutting the scaleni and all other thoracic muscles which might share in respiratory excursion. Only the upper intercostals and the diaphragm were left and the lungs were collapsed. Beau and Maissiat observed that under these conditions the diaphragmatic ribs were elevated and the base of the thorax was widened. When the diaphragm was hastily cut away the base of the thorax was immobilized. They confirmed Galen's observation, but said nothing about the rôle of the viscera underneath the diaphragm contributing to the spread of the lower thorax during inspiration. M. T. de Brou[2] repeated the experiments of Beau and Maissiat and came to just the opposite conclusion.

2. de Brou, M. T.: Gazz. Med., 1843, p. 344.

As we shall see later, the differing results of these observers was due merely to a difference in the vaults of the diaphragms of the dogs used by the experimenters. De Brou evidently used a dog which had less convexity to his diaphragm than had the dog which was used by Beau and Maissiat. Under the experimental conditions, a dog with a long thorax and high arch to his diaphragm would show an inspiratory widening of the subcostal angle, whereas a dog with a shorter thorax with less convexity to his diaphragm would show an inspiratory narrowing of the subcostal angle. The reason for this will be discussed later.

Up to the time of Duchenne, great doubt existed as to whether or not the diaphragm played any rôle in inspiratory widening of the base of the thorax. Since Duchenne's experiments, however, widening of the subcostal angle has been ascribed in part to diaphragmatic action. It is this error which has caused so much confusion and misinterpretation of the respiratory movements of the costal borders.

Duchenne applied electrodes over the phrenic nerve in front of the scalenus anticus and observed protrusion of the epigastrium and an outward movement of the costal margin on the affected side. This is an observation which is unreliable, because one could not be sure that the intercostals of the affected side were not also activated.

Duchenne then exposed the phrenic nerve of a dog and stimulated the nerve with an electric current and observed the same movements of the epigastrium and costal margin. This is contrary to the results which I[3] procured by stimulating the exposed phrenic nerves of dogs. We must, however, take into account that Duchenne's observations were made on dogs with unopened abdomens, whereas my observations were made on dogs with abdomens opened so I could see the movements of the diaphragm. In my experiments the costal margins were drawn violently toward the median line when the exposed phrenic nerves were stimulated by an electric current.

Duchenne repeated his experiments on both horses and dogs and got the same results, but in both horses and dogs, phrenic activation caused retraction of the hypochondria and narrowing of the subcostal angle when the abdomens were opened and all the viscera were removed from the upper abdomen. Duchenne says that such diaphragmatic activation has an expiratory result. We will see later that Duchenne's animals would have shown a narrowing of the subcostal angle from isolated phrenic activation had the abdominal wall been opened so as to allow the entrance and exit of air during respiration. It was not

3. Hoover, C. F.: The Functions of the Diaphragm and Their Diagnostic Significance, THE ARCHIVES INT. MED., 1913, **12**, 214.

necessary to disturb the abdominal viscera to change the direction in which the costal margins moved during phrenic contraction.

In a former communication[3] I described several experiments in which it was clearly proved that when the diaphragm was activated by electric stimulation the costal margins were violently drawn toward the median line. All these experiments, however, were made with the abdomen opened so the movements of the diaphragm were plainly visible from its lower surface.

In the meantime a patient suffering from fracture of the sixth cervical vertebra was observed, in whom there was complete motor paralysis of all muscles supplied below the sixth cervical segment. The scaleni and diaphragm were preserved, but all the intercostal muscles were paralyzed. During inspiration the first ribs were stationary and the hypochondria were retracted with each inspiration. The subcostal angle was much narrowed with each inspiration. The entire costal margins on both sides were drawn toward the median line with each contraction of the diaphragm.

Experiment 5.—A dog of the setter type was anesthetized with ether and then the cervical cord was sectioned at the sixth segment. To our surprise we found a respiratory movement of the thorax which was quite different from what we expected to find in view of our former experiments and clinical observations. The first ribs were stationary. There was only inspiratory retraction of the ribs and intercostal spaces in the upper thorax, but in the lower thorax there was a very different picture. From the ninth to the twelfth ribs inclusively there was an outward movement with distinct widening of the subcostal angle during inspiration. The character of the movement, however, was not such as we see when the intercostal muscles are active. The outward movement of the lower ribs was evidently a passive and not an active movement. The movement was quite like that observed by Beau and Maissait and by Duchenne in their animal experiments.

An incision was then made in the linea alba so the peritoneal cavity was opened and then a reverse movement in the lower ribs occurred. During inspiration the entire costal margins and hypochondria of both sides were drawn toward the median line. The abdominal wound was then clamped and the former inspiratory widening of the subcostal angle occurred. This observation was repeated a number of times until it was clearly apparent that removal of the viscera was not necessary to convert the inspiratory widening of the subcostal angle to inspiratory narrowing of the angle. When the abdominal wound was closed we evidently had the same physical conditions as before the incision was made.

The dog's diaphragm is more convex than the human diaphragm. The dog has thirteen ribs, and in some breeds of dogs, such as the setter, the thorax is particularly long, with a very acute subcostal angle. Such a conformation gives a high dome to the diaphragm, so that when the intercostal muscles are paralyzed, the subcostal angle widens during inspiration, because there is such a great disparity between the resultant line of traction of the diaphragm and the anatomic line of the diaphragm. The resultant line of traction is a straight line drawn from the central tendon to the costal margins where the

diaphragm is inserted. When the abdomen is closed, the respiratory descent of the diaphragm is attended with an increase in intra-abdominal pressure which is transmitted equally in all directions. If the lateral pressure in the abdominal cavity produced by descent of the diaphragm exceeds traction on the costal margins, then the hypochondria will spread during inspiration, although the intercostal muscles may be paralyzed. When there is an opening in the epigastrium, then descent of the diaphragm simply displaces the air and does not increase the intra-abdominal pressure; consequently there is no pressure to counterbalance the traction on the costal margins and the entire costal margin is drawn toward the median line. It will be observed also, that when the intercostal muscles were paralyzed in this particular dog, only the ninth, tenth, eleventh and twelfth ribs moved outward; the sixth, seventh and eighth ribs were stationary. This was due to the varying curve of the diaphragm in its different parts. The anterolateral portion of the diaphragm has less convexity than those fibers in the lateral portion which are inserted in the lower ribs. Consequently, the less disparity there is between the curve of the fibers and the straight line of resultant traction, the more advantage will traction acquire over any force which tends to move the costal ends or ribs away from the median line.

This was proved by repeating the experiment on a dog of the bulldog type, which has a shorter thorax and less acute subcostal angle than in the dog used in the experiment just described. When the intercostal muscles were paralyzed by section of the dorsal spinal cord at the fourth dorsal segment, all the intercostal muscles below this level were paralyzed, but unlike the previous experiment, the entire costal margins on both sides were drawn toward the median line. The movement of the costal margins was unchanged by opening the abdomen. In this manner I believe we can account for the time honored experiments of Duchenne, and also for the differing results obtained by his predecessors. Duchenne evidently used dogs with a high arch to the diaphragm, and so did Beau and Maissiat, but de Brou, in his experiment, employed a dog with less convexity of the diaphragm and observed both costal margins drawn toward the median line during inspiration. Thus it seems that finally we have a satisfactory explanation for the conflicting results obtained by different experimenters who have studied the function of the diaphragm.

I have never seen an instance of paralysis of the intercostal muscles in man which was attended with inspiratory widening of the subcostal angle and spreading of the hypochondria. This is due to the fact that the dome of the diaphragm is not sufficiently arched to permit the inspiratory increase of pressure within the abdomen to exceed the diaphragmatic traction on the costal borders during inspiration.

The significance of the arch of the diaphragm for inspiratory movements of the costal margins was fully discussed in a publication by me[3] in 1913. Since that time there has been gathered much confirmatory evidence.

I have had three experiences which prove the correctness of the idea that the true explanation lies in the disparity between the resultant line of traction and the curve of the diaphragm, and not in the height of the diaphragm. If the curve of the diaphragm is responsible for the outward movement of the costal borders during inspiration, then it is obvious that the costal margin should diverge from the median line when the diaphragm is convex on its under surface as well as when it is convex on its upper surface.

This was observed to be a fact in two cases of thoracic empyema of the left side in which the normal spleen was displaced below the costal border by the downward displacement of the diaphragm. In both cases there was inspiratory divergence from the median line by the left costal border. One quart of pus was then aspirated and then the left costal margin was drawn toward the median line during inspiration. Later, two quarts more of pus were aspirated, whereupon the left costal margin diverged from the median line. When the line of traction and the plane of the diaphragm coincided, that is, when the diaphragm was arched neither upward nor downward, then the acting diaphragm gained the mastery over the costal border against the antagonists, namely, the intercostal muscles. When the diaphragm was arched either upward or downward, then there was sufficient disparity between the resultant line of traction of the diaphragm and the plane of the diaphragm so that the diaphragm's antagonists (the intercostal muscles) gained the mastery of the costal margin and the rib margin moved away from the median line during inspiration.

These cases also prove the incorrectness of the idea of the piston descent of the diaphragm during inspiration being the cause of the inspiratory spread of the hypochondria. When the left diaphragm was convex on its under surface its contraction caused a lengthening of the abdominal cavity instead of the normal shortening, so there could have been no inspiratory increase of the intra-abdominal pressure from activation of the left diaphragm. In spite of this fact, the costal margin moved away from the median line during inspiration just as when the diaphragm was convex on its upper surface.

There are other reasons to prove that in man the piston-like descent of the diaphragm is not a factor in the inspiratory widening of the subcostal angle. The curves of different groups of fibers in the diaphragm vary greatly. There is much less curving of the fibers which pass from the central tendon of the diaphragm to the costal margin near the median line than there is in those fibers which pass from the

central tendon to the costal border in the axillary line. We see the line of the diaphragm at its sternal portion more nearly approaches a straight line than at any other part. The anterolateral part of the diaphragm requires less depression to give this part of the diaphragm a horizontal position than is required to accomplish the same for parts occupying a more lateral position. The anterolateral part of the diaphragm has a slight curve to its fibers from origin to insertion; it is very near the critical position, so that very slight depression is required to give this portion of the diaphragm the mastery over that portion of the costal margin where it is inserted.

When the heart or pericardial sac is enlarged to a moderate degree, that part of the costal margin from the median line to the ninth costal cartilage will be drawn toward the median line during inspiration; but beyond this median half of the costal margin, the inspiratory movement is in a lateral direction. On several cases I have observed the reverse of this when the posterolateral portion of the pleural sinus was filled with fluid. The subcostal angle widened during inspiration, but the lower and lateral portion of the costal border was retracted.

When the entire lung is emphysematous to a sufficient degree to cause retraction of any portion of the costal margin, the entire margin is retracted. Under these conditions there is inspiratory narrowing of the subcostal angle and inspiratory retraction of the whole of both costal borders.

In my former communication the importance of this sign was pointed out as the only method of estimating the higher degrees of emphysema. Moderate emphysema of the pulmonary borders may fill the pleural sinuses so that lung resonance will descend to the bottom of the pleural sinus in the anterior, lateral and posterior lines, but if the great body of the lung is not emphysematous, there will be no inspiratory narrowing of the subcostal angle. For example, a patient with chronic bronchitis and emphysema will have the lower borders of the lungs at the eighth, tenth and eleventh ribs, respectively, in the anterior, axillary and scapular lines, and have no respiratory discomfort or inspiratory retraction of any part of the costal margins; on the following day the man may have cyanosis and dyspnea with a rise of 2 per cent. in the carbon dioxid concentration of the alveolar air. The percussion borders of the lungs are unchanged, but the body of the lung is much larger, and the only physical sign of this enlargement will be inspiratory narrowing of the subcostal angle and inspiratory retraction of the entire costal margin of both sides.

Furthermore, this differentiation between depression of the anterolateral portion alone of the diaphragm from depression of the entire diaphragm is important in estimating the pulmonary and cardiac sources of air hunger. It is not at all uncommon to see patients with

moderate emphysema whose hearts are enlarged. The percussion borders of the lung may reach to the bottom of the pleural sinuses, but if there is only inspiratory narrowing of the subcostal angle, and the costal margins below the ninth costal cartilages move laterly during inspiration, then the patient's air hunger is not due to emphysema, for when air hunger from emphysema exists there will be not only inspiratory narrowing of the subcostal angle, but there will be inspiratory retraction of the entire costal margin.

A careful study of the subcostal angle is also important to determine the symmetry or asymmetry of movement of the two costal margins in their upper or median portions.

If the patient should have enlargement of the left ventricle alone, as in cases of arterial and aortic valve disease, then the median portion of the left costal margin will be retracted or move less in an outward direction during inspiration than the symmetrical part on the right.

In cases of mitral stenosis, myocardial disease, and enlargement of the pericardial sac there will be symmetrical narrowing or constraint of the subcostal angle during inspiration if the anterolateral portion of the diaphragm is depressed beyond the critical point. These points are all specifically mentioned because I have found that an analysis of the respiratory movements of the subcostal angle and costal borders has been of much service in arriving at an estimate of the relative enlargement of the two sides of the heart, enlargement of the pericardial sac and enlargement of the entire body of the lungs.

In a routine examination it is important to determine the symmetry or asymmetry of movement in the subcostal angle and lower costal margins and the relation of their movements to the median line. When the arch of the diaphragm is accentuated, as in cases of hepatic enlargement or subphrenic accumulations of pus or serum, then the outward movement of the costal border on the affected side is increased. Accentuation of the diaphragmatic arch and fixation of the diaphragm to the thoracic wall were discussed in a former article;[3] so I shall refrain from discussing this phase of diaphragmatic action any further than to describe a single experience of recent date in which the balance between the intercostal muscles and diaphragm was clearly illustrated. The patient had an acute suppurative pylephlebitis which produced a moderate enlargement of the liver in an upward direction. The patient had violent and protracted hiccough in which the diaphragm and intercostals were both activated. On the left side the costal margin was drawn toward the median line with each hiccough; on the right side the costal margin moved away from the median line with each hiccough. At the necropsy nothing was found to account for this asymmetry of

movement of the costal margins excepting a very moderate enlargement of the liver in an upward direction.

In studying the respiratory movements of the base of the thorax we must differentiate between evidences of phrenic activation and phrenic excursion.

The Litten diaphragm phenomenon is an evidence of phrenic excursion and is a supraphrenic phenomenon which is present only under normal conditions, or conditions which approximate the normal. The sign is not present under abnormal conditions.

The direction of movement and comparative movements of the median and lateral portions of the costal margins on the two sides give us valuable information on activation of the diaphragm and the position of its median and lateral parts. The direction in which any portion of the costal margin may move is determined by the resultant of two forces. One is the expression of the action of the intercostal muscles, which always widens the subcostal angle and spreads the hypochondria; the other force originates in activation of the diaphragm and always draws the costal margin toward the median line. When the resultant of these two forces causes narrowing of the subcostal angle, the subcardial or median portion of the diaphragm is less convex than normal. When the entire costal margin is drawn toward the median line, the entire phrenic leaf has lost a large part of its convexity. The movement of the costal margins has nothing to do with excusion of the diaphragm; it is merely the resultant of activation of the intercostal muscles and of the diaphragm. The only subphrenic sign of phrenic excursion is protrusion of the epigastrium and lateral portions of the abdomen.

The significance of the slight arch of the anterolateral portions of the diaphragm is illustrated very nicely in cases of acute cardiac dilatation due to myocardial incompetence from arterial sclerosis. It is a common experience to see these patients brought to the hospital with dilatation of both sides of the heart. During this period there will be symmetrical inspiratory narrowing of the subcostal angle, but the lower and lateral portions of the costal margins move away from the median line during inspiration. As the heart recovers from its acute dilatation, the upper and inner half of the right costal margin will resume its outward movement during inspiration, but the left side of the subcostal angle will be restrained in its outward movement or may continue to move toward the median line during inspiration. This is, of course, due to the fact that the left ventricle is permanently enlarged and depresses the left sternocostal portion of the diaphragm. The symmetry and asymmetry of movement of the two sides of the subcostal angle and the lower and outer halves of the costal margins give

much valuable information concerning the total volume of the lungs, and form and size of the heart and heart's sac. Furthermore, an exact analysis of the respiratory movement of each part of the thoracic cage is essential to form an adequate estimate of the ventilatory function of the different parts of the lungs. Such an analysis is also necessary to form an exact idea about the factors in supraphrenic and infraphrenic diseases which may modify the curve in any part of the diaphragm.

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SERUM CHANGES FOLLOWING PROTEIN "SHOCK" THERAPY *

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The degree of interest with which certain phases of therapeusis along nonspecific lines has been received would seem to indicate that clinical observation of such character must have been quite frequently, although the possible significance had escaped comment. Various German clinicians have, in recent times, emphasized the striking therapeutic effects achieved with this so-called "protein" therapy, a not inapt designation, conveying, as it does, not only the concept of the basic reacting agent, but implying, too, wide range of effectiveness as a therapeutic measure. The best results have undoubtedly been obtained in the arthritic processes, an extended series of observations on such cases having been published by Miller and Lusk,[1] and Culver.[2] They seem particularly favorable for treatment, because the contraindications are few and the objective and subjective evidence of improvement under treatment are directly observable.

In a paper published last year Jobling[3] discussed some of the factors that were possibly operative following intravenous protein therapy, basing his views on an extended study in experimental animals. The changes in the blood pressure and the blood cytology have been studied by Scully[4] in Miller's Clinic, and inasmuch as Culver[5] has followed the changes in antibody formation, these phases are not covered in this paper, which is limited to the study of certain ferment and physical alterations following protein injections.

When the normal or diseased organism is subjected to a protein shock of whatsoever origin — bacterial, protein split products, milk, etc. — certain fundamental but as yet intangible alterations occur in the organism, as a result of which an increased resistance to infection

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1. Miller, J. L., and Lusk, F.: The Use of Foreign Protein in the Treatment of Arthritis, Jour. Am. Med. Assn., 1916, **67,** 2010.
2. Culver, H.: The Treatment of Gonorrheal Infections, Jour. Am. Med. Assn., 1917, **68,** 362.
3. Jobling, J. W., and Petersen, W. F.: The Nonspecific Factors in the Treatment of Disease, Jour. Am. Med. Assn., 1916, **66,** 1753.
4. Scully, F. J.: Jour. Am. Med. Assn., 1917, **69,** 20.
5. Culver, H.: Jour. Lab. and Clin. Med., October, 1917, **2.**

and to intoxication is definitely established. The terms "antianaphylaxis" and "desensitization" applied to this state convey certain ideas of specificity and are therefore not quite suited; the German "umstimmung" possibly expresses the fundamental character of the changes involved, and von Groer[6] has coined the term "ergotropie" to cover the new therapeutic conception whereby we seek to change the reactivity of the host through a biologic reaction rather than directly to alter or destroy the invading parasite.

In its essentials, the state of antianaphylaxis, or the refractory period following anaphylactic shock, is found to occur after all varieties of protein shock. Vaughan[7] noted this resistance following the injection of his protein split products; Zinsser and Dwyer[8] have discussed it in its relation to proteophylatoxin or anaphylatoxin; Jobling[9] observed it to occur after serotoxin injections and Tigue and McWilliams[10] have recently observed the increased resistance to typhoid infection in rabbits after a typhoid vaccine shock. It has been known for some time, of course, that antianaphylaxis is relatively nonspecific, insofar as following recovery from a nonfatal shock dose in a doubly sensitized animal the sensitization to the second antigen is greatly reduced. Bessau[11] and his associates have fully discussed this subject. Inasmuch as the "ergotropie" observed in these newer therapeutic studies is also nonspecific, its relation to the antianaphylactic condition is at least made probable.

In a series of studies made some time ago, Jobling[12] and his associates found that anaphylactic shock (and the protein intoxications in general) was accompanied in dogs by marked changes in the blood ferment-antiferment balance. It seemed warranted to assume that, at least in such animals, the shock involved both cellular and humoral factors; that the cellular reaction was probably the primary one, and that the serum reactions that followed brought about further intoxication and death. It was observed that during shock a condition obtained (low antiferment and increased protease) when proteolytic activity was favored, while following shock the reverse held true (increased antiferment and low protease). During this refractory period reinjection is followed by no change in the ferment-antiferment balance. Rusznjak[13] was the first to observe the change in the antiferment, and

6. von Groer: München. med. Wchnschr., 1915, **62,** 1312.
7. Vaughan, V. C.: Protein Split Products, 1913, Lea & Febiger, Philadelphia and New York.
8. Zinsser, H., and Dwyer, J. A.: Jour. Exper. Med., 1914, **20,** 387.
9. Jobling and Petersen: Jour. Exper. Med., 1914, **19,** 480.
10. Tigue, O., and McWilliams, H.: Jour. Immunol., 1917, **2,** 167.
11. Bessau, G., Opitz and Preusse, O.: Zentralbl. f. Bakt., Part 1, Orig., 1914, **74,** 162 and 310.
12. Jobling, Petersen and Eggstein: Jour. Exper. Med., 1915, **22,** 401.
13. Rusznjak, S.: Deutsch. med. Wchnschr., 1912, **38,** 168.

suggested its possible significance in the phenomena of resistance following shock.

Friedberger and his school have developed the ideas originally presented by Matthes, and by Vaughan in this country, concerning the relation of fever to protein intoxication. According to this conception, which is based on a vast accumulation of experimental evidence, the invading organisms themselves, unless they happen to excrete a definite toxin, cause no marked intoxication of the host until the host becomes sensitized to the bacterial protein derived from disintegrated organisms. This state is ushered in by the febrile reaction. Freedom from symptoms could then occur either (*a*) when the host is desensitized, or (*b*) when the parasites are destroyed; it is clear that the first supposition need not imply the destruction of the infecting organisms. Unfortunately, in this relatively simple conception another factor is manifest, namely, that from the bacteria are derived not only native proteins that sensitize the host, but protein split products as well, which are able to intoxicate the host directly. During the refractory period the resistance to these is also increased, but the chief agent in ridding the system of this poison would be proteolytic ferments of the peptidase or ereptase type, which would hydrolyze these toxic products to the lowest and nontoxic form. From these considerations it is apparent that if in typhoid fever, for instance, protein shock is induced and the disease terminated by crisis, the infecting organism need not be destroyed, the host may be simply desensitized so that the condition in a manner resembles the period of incubation during which time organisms may be abundantly present, but cause no reaction. That this is actually the case is indicated in several reports from German workers who have obtained positive blood cultures and stool cultures in typhoids a considerable period of time after all disease manifestations had subsided following intravenous shock therapy; the patients being afebrile, the spleen small and the diazo reaction negative.

With these considerations in mind, it would seem pertinent to ascertain just what changes do occur in the serum of patients following protein therapy and in how far such changes may account for the therapeutic benefit derived.

EXPERIMENTAL

The serum changes studied included the following:

(*a*) Stalagmometric
(*b*) Concentration of serum (total nitrogen)
(*c*) Noncolloidal nitrogen of serum
(*d*) Antiferment
(*e*) Serum protease. (Chloroform method at 47 C.)
(*f*) Serum ereptase. (Peptone splitting at 47 C., tryptophan reaction)
(*g*) Serum diastase (Wohlgemuth method)
(*h*) Serum esterase (Michaelis-Rona and ethyl butyrate methods)

The proteins injected were either typhoid bacilli in doses varying from 25 to 150 million (fresh vaccine) or albumoses; primary and secondary proteoses fractionated from Witte peptone. The latter, in doses from 40 to 60 mg. give a satisfactory reaction. The protocols selected are representative of the changes observed in a large series of cases.

(*a*) As a result of the peripheral vasodilation and the profuse sweating that normally follows protein shock, appreciable changes occur in the concentration of the blood serum, which in turn is reflected in the rate of the flow through the stalagmometer, as shown in the following determination:

J. P. Monarticular rheumatism. Typhoid vaccine injection.

Rate of flow before injection.....	12.8 drops per minute
Rate of flow 2 hours after injection...	12.0 drops per minute
Rate of flow 8 hours after injection...	11.4 drops per minute
Rate of flow 24 hours after injection...	10.6 drops per minute
Rate of flow 72 hours after injection...	11.3 drops per minute

(*b*) The concentration of the serum proteins is increased following the injections; for comparison the corresponding stalagmometric readings are shown together with the Kjeldahl titration for 2 c.c. of serum.

J. B. Acute arthritis. Typhoid vaccine injection.

Stalagmometric Readings		Fifth Normal Hydrochloric Acid, Kjeldahl Titration for 2 C.c. Serum
Before injection	10.7 drops	6.2 c.c.
3 hours after injection....	10.0 drops	6.27 c.c.
6 hours after injection....	9.3 drops	6.5 c.c.
18 hours after injection....	9.2 drops	6.975 c.c.

The change in the stalagmometer readings must depend largely in this case on the alteration of the concentration of the serum which may be of sufficient magnitude to mask smaller changes that might be expected to result from changes due to alterations of the dispersion of the serum colloids.

(*c*) The nonprotein nitrogen of the serum remains practically unaltered, as shown in the following two cases:

H. L. Acute arthritis and pharyngitis. R. C. Acute arthritis, with possible endocarditis; both received typhoid vaccine intravenously.

	H. L. Mg. Per C.c.	R. C. Mg. Per C.c.
Blood before injection.....	0.5	0.47
Blood 3 hours after injection.....	0.5	0.45
Blood 18 hours after injection.....	0.55	0.47
Blood 72 hours after injection.....	0.5	0.47

It is evident that no retention of nonprotein nitrogen takes place as a result of possible injury to the cells of the excretory apparatus, which coincides with the urinary examination made on cases following protein shock; that is, no albuminuria occurred unless already present before the injections and in these cases no increase in the amount of albumin was noted.

(*d*) The changes in the antiferment of the blood serum are usually well marked and quite uniform in the cases that react favorably to the shock therapy. Chart 1, A illustrates the changes taking place for a three-day period of observation in a case with complete recovery from an acute arthritis following intravenous injection of 60 mg. of a primary proteose. The persistence of the increased antiferment titer may be much less in duration, as shown in the second Chart 1, B. This case, K.H., was one of multiple subacute arthritis which did not improve to any marked extent after injection of typhoid vaccines, although there was temporary relief.

Finally, the cases that show no permanent improvement seldom show any increase in the antiferment, indeed almost always present a decrease in the titer following the shock, as illustrated in the third and fourth charts, 1, C and 1, D.

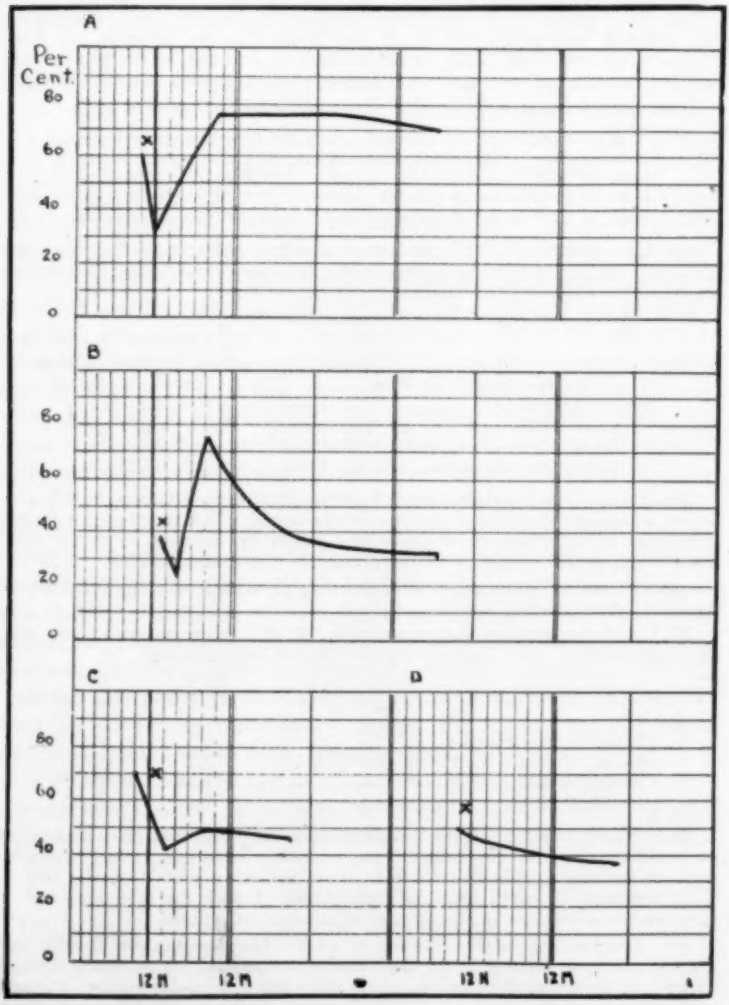

Fig. 1.—Changes in antiferment titer following protein shock. × indicates injection.

(*e*) The serum protease is almost invariably decreased immediately following the shock, but later increases progressively for a period of two or three days, as shown in the following tabulations in which the titer of the ferment

is expressed in the amount of serum protein digested in 1 c.c. at 47 C. when emulsified with chloroform. The titer for the first eighteen hours following injection in an acute arthritis, G. W., with complete recovery, was as follows:

Before injection	0.08 mg. per c.c.
2 hours after injection	0.02 mg. per c.c.
6 hours after injection	0.07 mg. per c.c.
18 hours after injection	0.06 mg. per c.c.

H. L. Acute arthritis; typhoid vaccine.

Protease before injection	None demonstrable
Protease 3 hours after injection	None demonstrable
Protease 18 hours after injection	0.03 mg. per c.c.
Protease 48 hours after injection	0.2 mg. per c.c.

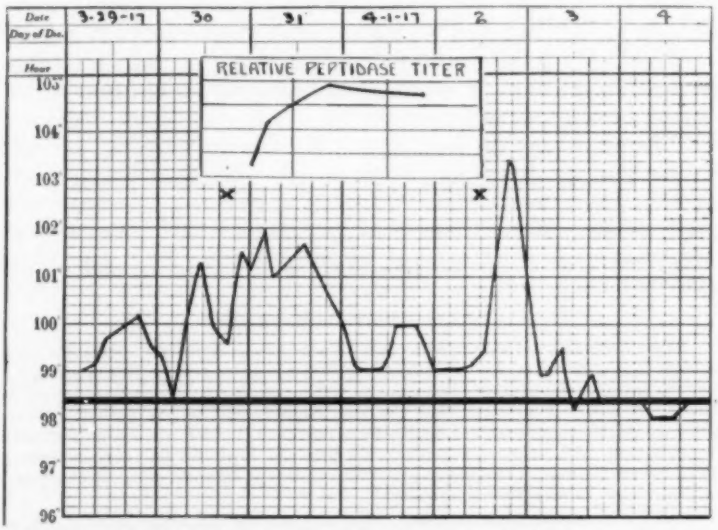

Chart 2.—Peptidase titer following protein shock. × indicates injection.

(*f*) The serum ereptase or peptidase is almost invariably increased in those cases that respond to vaccines with clinical improvement, the maximum concentration being reached after twenty-four hours.

J. C., white man, with physical findings of diffuse bronchitis, had persistent irregular temperature for the two weeks he was under observation, with no signs of improvement. Two doses of typhoid vaccine were given intravenously, following which marked clinical improvement occurred, together with clearing of physical findings and an afebrile temperature curve. The relative peptidase titer observed in the serum following the second dose of vaccine is illustrated in Chart 2.

A. G. Multiple acute arthritis. Typhoid vaccine was administered, with complete recovery. The peptidase titer in this case was as follows:

	Serum			
	0.5 C.c.	0.25 C.c.	0.125 C.c.	0.0625 C.c.
Before injection	+++	+++	+	—
6 hours after injection	++++	++++	+	—
24 hours after injection	++++	++++	++	+

The majority of cases that show no clinical improvement give no evidence of an increase in peptidase; this is illustrated in the following patient:

J. S. Gonorrheal rheumatism (knees and ankles) of several months' duration, with subacute prostatitis. Three c.c. 2 per cent. proteose was injected, resulting in well marked reaction but no clinical improvement.

	Serum	
	0.5 C.c.	0.25 C.c.
Peptidase titer before injection.....	+	+
After twenty-four hours.....	+	—

There being no clinical improvement, the patient was given three injections of typhoid vaccine without benefit. Gonococcus vaccine was then tried, without effect. The patient was relieved to a greater extent by iodids given intravenously than with any other measure, but did not make a complete recovery until he had developed an intercurrent peritonsillar abscess, following which the joint symptoms cleared completely.

(*g*) Diastatic activity. This ferment is almost invariably diminished after the shock and the titer may remain low for several days thereafter.

J. P. Monarticular arthritis.

Diastatic titer before injection.....	$D\frac{37°}{24\ Hrs.} = 32$
3 hours after injection.....	D = 16
6 hours after injection.....	D = 16
18 hours after injection.....	D = 8

(*h*) The study of the lipolytic activity (esterase titer) revealed no consistent alterations.

RESISTANCE TO REINJECTION

When the patient is subjected to two or more doses of vaccine intravenously, evidences of resistance are occasionally noted, not only against the shock effect —chill, fever and sweating—but also to some extent against further beneficial effect. It is our impression that the maximum benefit to the patient follows the first injection, although undoubtedly a number of cases will show continued improvement with reinjections when the primary injection did not completely clear up the disease. The resistance which develops is nonspecific in character, as illustrated in the following case:

C. H. Acute multiple arthritis. He received at intervals three doses of typhoid vaccine, each from fifty to seventy-five million, intravenously. The patient was improved, but still complained of some stiffness of the ankles. At this time it was observed that the injection of a dose of the same amount was followed by no reaction. The serum examination made at this time showed a relatively high antiferment titer—0.01 c.c. of serum inhibiting 80 per cent. of the trypsin unit; ereptase was present in a moderate amount, 0.125 c.c. serum giving a good tryptophan reaction in twenty-four hours' digestion at 47 C.; and the serum contained protease—0.08 mg. digestion per cubic centimeter in twenty-four hours at 47 C. These changes, while definite, were, however, identical with those observed in cases not resistant to reinjection; so that we are forced to conclude that the resistance must be largely cellular in character.

DISCUSSION

From the observations described it is evident that the reaction of the host which follows protein shock therapy is accompanied by definite serum changes, including a mobilization of both protease and ereptase,

alterations in the antiferment titer, as well as certain physical changes. It is to be emphasized that these changes are not to be considered as wholly responsible for the therapeutic effect observed following shock therapy; indeed, we are under the impression that they should be regarded rather as an index of cellular changes which are the primary ones concerned; but inasmuch as the means of investigation of direct cellular changes are limited, the serum changes may be considered as offering at least some tangible object for study. Culver has recently followed the antibody changes following intravenous vaccine therapy. He finds an increase in the specific bacteriolysin and opsonin (gonococcus) following injections of gonococcus vaccines (as well as proteoses), an increase most marked after the first injection; with subsequent injections a decrease may be observed, despite continued improvement of the patient. Practically the same may be said of the proteolytic serum ferments. A mobilization takes place after the injection, but following injections may be followed by no such change. On the other hand, the cases that do not show clinical improvement seldom show an increase in peptidase, thus differing from the antibody observations. The ereptase may be considered a detoxicating agent which aids in the elimination of the toxic products of the pathogenic organism, while the antibody mobilization may be responsible for the actual destruction of these organisms.

The mobilization of the ferments is much less prompt than in experimental animals, nor is it directly proportional to the severity of the chill or the degree of the temperature reaction, although as a rule the clinical improvement is more apparent when a good febrile reaction is elicited.

It is of course well known that the thorough sweating of a patient will of itself afford marked relief of arthritic symptoms, but relief is practically always transient. It is probable that the immediate relief which follows shock therapy in these cases is due to a similar cause, the difference lying in the permanancy of the cure. It is reasonable to suppose that in this the mobilization of the leukocytes and antibodies and ferments is of importance.

The changes in the antiferment have been discussed previously; following the initial decrease a rise takes place which in the favorable cases persists for from two to seven days, while in the cases that show no clinical improvement the increase has been found to be transient or to be lacking altogether.

As will be discussed in a following paper, an increased antiferment titer is commonly associated with an increased resistance to protein intoxication, the increase either itself protecting the cells or at least being indicative of cellular changes associated with an increased resist-

ance. Whether there exists a possible direct relation to bacterial proliferation is a question that has not as yet been thoroughly studied. Wright[14] has carried out some experiments along this line, but his investigations were concerned chiefly with the bacterial flora of wounds and the relation of the leukoproteolytic ferments and antiferment thereto.

Tigue and McWilliams[15] have suggested that the therapeutic effect may depend on an increased passage of antibody containing serum into the lymph channels. In experimental animals Davis and I[16] have, indeed, found that a marked augmentation of the flow from the thoracic duct does occur following shock, so that the suggestion is one that may have considerable bearing on the subject.

We believe it is at present justifiable to consider that the benefits of shock therapy do not depend on any single alteration in the reacting organism, but on a series of factors in which not only the serum antibody and ferment changes, but the leukocytosis, the fever and sweating and the increased lymph flow have a part along with the important cellular changes which are as yet intangible.

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14. Wright, A.: Brit. Med. Jour., 1915, **2**, 629.
15. Tigue and McWilliams: Jour. Immunol., 1917, **2**, 193.
16. Davis, B. F., and Petersen, W. F.: Jour. Exper. Med., 1917, **26**.

VENTRICULAR FIBRILLATION IN MAN WITH CARDIAC RECOVERY*

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ST. LOUIS

The interest in ventricular fibrillation as a disturbance of the cardiac activity of man has been centered about the rôle this phenomenon may play in causing sudden death. It has been generally accepted that when the human ventricles pass into a state of fibrillation, death is an almost immediate and invariable consequence.

Ventricular fibrillation can be determined definitely by electrocardiograms, as its presence is indicated by a well defined type of record. This type has been frequently obtained from animals in which ventricular fibrillation was directly observed in the exposed heart. The usual waves that are produced by the passage of the excitation impulse through the ventricles and the resulting contraction disappear and in their place rapidly recurring, more or less irregular, waves occur following each other so closely that no period of cardiac inactivity is indicated. The waves vary in height and in form, and short stretches during which they are of diminished size are apt to occur at intervals in the records.

Although ventricular fibrillation may be a frequent cause of sudden death of man, very few electrocardiographic records have been obtained which signify its presence, because it is necessarily transient, as it is in most instances incompatible with life. Records obtained by one of us[1] from seven patients at the time of death from various causes indicated that fibrillation of the ventricles preceded briefly complete cardiac arrest in one and possibly two instances. A characteristic record of ventricular fibrillation was also obtained by Halsey[2] in one case at the time of death, while Hoffman[3] has published a record which he interprets as indicating the brief occurrence of ventricular fibrillation ter-

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* From the Department of Internal Medicine, Washington University Medical School.

* Read at the meeting of the Association of American Physicians, May 2, 1917.

1. Robinson: A Study with the Electrocardiograph of the Mode of Death of the Human Heart, Jour. Exp. Med., 1912, **16**, 291.

2. Halsey: A Case of Ventricular Fibrillation, Heart, 1915, **6**, 67.

3. Hoffman: Fibrillation of the Ventricles at the End of an Attack of Paroxysmal Tachycardia in Man, Heart, 1912, **3**, 213.

minating in recovery at the end of an attack of paroxysmal tachycardia. His interpretation is questioned by Lewis,[4] and Hart[5] and others.

These few records constitute the entire direct evidence that ventricular fibrillation occurs in man. The belief of its occurrence beyond this evidence is based on conjecture and analogy with experimental results. The question of its occurrence and its importance as a cause of sudden death has been discussed by Lewis[4] who says that he has the strongest *a priori* grounds for the belief that sudden death results from ventricular fibrillation in many patients. He points out that when

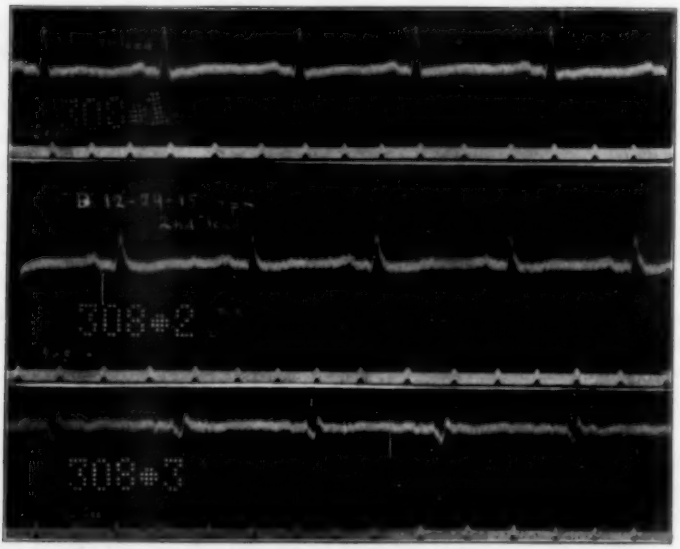

Fig. 1.—Three usual leads, obtained on day of admission, Dec. 29, 1915.

the ventricles fibrillate, the coordinate beat of these chambers is lost; the muscle is divided up into small areas, which show independent activities. This type of activity is functionally entirely ineffectual and the cardiac output ceases, the blood pressure falls to zero and the circulation comes to a standstill.

The observations to be reported here were made on a patient who had a series of attacks of prolonged cardiac syncope, closely resembling Stokes-Adams syndrome, from which she recovered. An electrocar-

4. Lewis: Observations on Cardiac Syncope, Lectures on the Heart, New York, 1915, p. 113.

5. Hart: The Diagnosis and Treatment of Abnormalities of Myocardial Function, New York, 1917, p. 171.

diogram obtained during one of these attacks is typical of ventricular fibrillation, and it seems likely that all syncopal attacks were of the same nature. This observation represents, therefore, recovery from at least one relatively prolonged period of ventricular fibrillation, and probably recovery from several such periods.

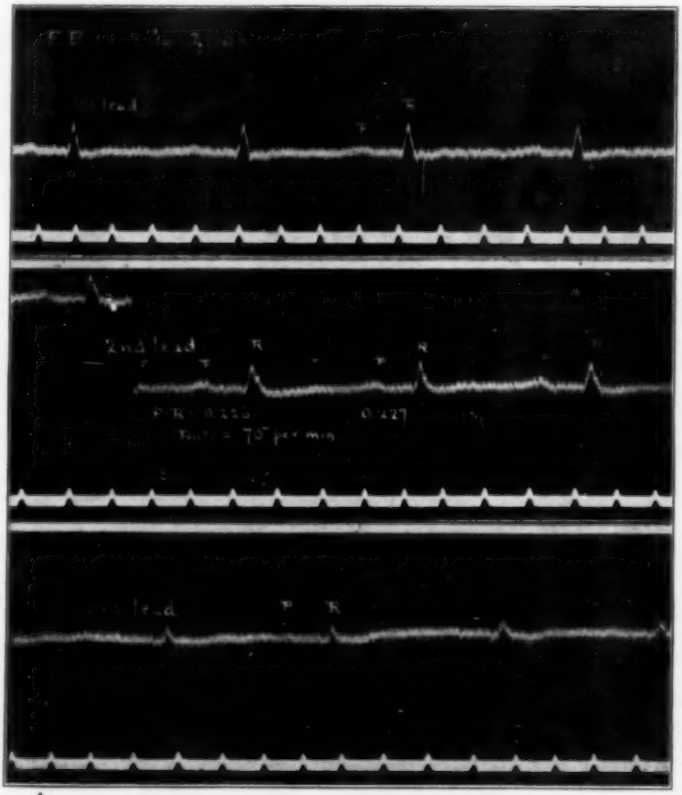

Fig. 2.—Three usual leads, Jan. 4, 1916. Eight minutes before onset of ventricular fibrillation.

REPORT OF CASE

History.—F. B., a woman aged 45, was admitted to the Barnes Hospital, Dec. 29, 1915, complaining of shortness of breath, swelling of the feet, weakness and cough. The family history is irrelevant. She had had three attacks of rheumatism at the ages of 14, 20 and 30 years, and had chorea at 9 years. She had also had typhoid fever in childhood and scarlet fever at 20 years of age. During her first attack of rheumatism she was told her heart was affected. There was no history of a surgical operation, nor any evidence of syphilis.

She had been short of breath on exertion as long as she could remember, and had been very pale and "anemic" for fifteen years. Swelling of the feet had been present for about one month, during which time dyspnea became more marked. She had slept with her head elevated for many years, but had been coughing for only about three or four weeks. She had had polyuria for about a year.

Physical Examination.—Physical examination revealed a pale, fairly well nourished woman, who seemed in no great distress or danger. Slight cyanosis was observed. The heart was slightly enlarged. The apex beat was in the fifth interspace, 12 cm. to the left of the midsternal line. The cardiac dulness extended 3 cm. to the right and 13 cm. to the left of the midsternal line. There was a presystolic thrill over the apex as well as a presystolic and systolic murmur. The heart rate was 81 per minute and regular. Fine moist râles were heard over the bases of the lungs posteriorly. The liver was not palpable. A uterine tumor was present, and there was slight edema of the feet, legs and thighs. The systolic blood pressure was 138 mm. Hg, diastolic 72 mm. Hg. The blood examination showed 2,944,000 erythrocytes, and 29,200 leukocytes per cubic millimeter, and hemoglobin 30 per cent. (Sahli instrument). Albumin and casts were found in the urine. The excretion of phenolsulphonephthalein amounted to 43 per cent. in two hours. During the first six days in the hospital the patient's condition improved somewhat and she seemed in a fairly satisfactory condition. The pulse ranged from 75 to 100 beats per minute. The temperature was slightly elevated at times, but gradually subsided. A blood culture remained sterile.

Subsequent Course.—Jan. 4, 1916, a pelvic examination was made per rectum. Shortly after the examination the patient was observed by the nurse to become suddenly unconscious "for a few minutes." She made jerking movements of her arms. The eyes were closed and the pulse was imperceptible. The intern, Dr. Fuson, was called immediately and when he arrived the pulse was weak and irregular. The patient was very blue and the feet were cold. The pulse became regular in a few minutes and beat fairly strongly at a rate of 68 per minute. The area of cardiac dulness was not increased. The presystolic and systolic murmurs were heard at the apex region as before. There was a hemorrhage in the conjunctiva of the left eye. The mental condition was clear and the patient was not suffering.

About one hour later, at 2:48 p. m., the patient was observed by the intern to become suddenly unconscious, when electrocardiograms were being taken. The pulse disappeared from the wrist, and the patient became very cyanotic. Breathing, except for occasional gasps, ceased for a period estimated at two or three minutes. The heart beat was inaudible at the apex.

The heart beat returned after being apparently absent for about four minutes, and in about fifteen minutes the heart was beating almost regularly at a rate of 85 to 100 per minute. During this time the breathing was slow, deep and snoring. The arms and feet were frequently stiffened out in convulsive-like movements. The reflexes of arms and legs were active. The pupils were pinpoint in size and there were irregular ocular movements.

At 5 p. m., two hours after the onset of unconsciousness, the patient became very noisy. She was still unconscious, but tossed her arms, head and feet about continually. She became quiet at 7 p. m., and at 8:30, although still unconscious, was breathing quietly, at times suggesting Cheyne-Stokes breathing. The pulse was irregular, about 80 per minute. The thrill could not be felt, and the heart sounds were very confusing to the ear.

At 11 p. m. the patient had her third convulsion. She became suddenly cyanotic and the heart-beat became inaudible. Breathing ceased for four minutes, the heart sounds disappearing before breathing stopped entirely. The breathing returned slowly, at first only 3 or 4 per minute, then gradually increasing up to 20 per minute. The heart beat returned very slowly, with

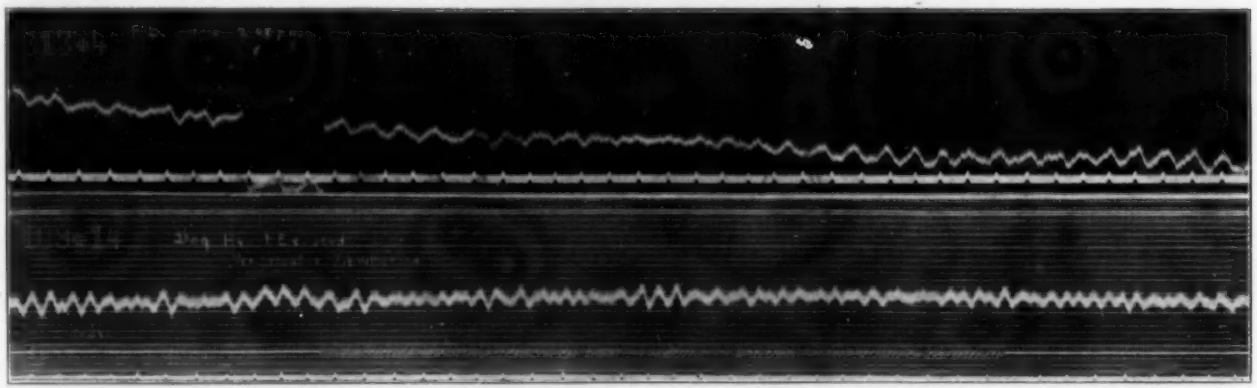

Fig. 3.—Upper curve. Record obtained during period of cardiac syncopy at 2:48 p. m., Lead 2. Lower curve from dog. Ventricular fibrillation observed in the exposed heart. Lead from right fore leg and left hind leg.

an increasing rate. The heart rate in successive minutes was 27, 41, 35 and 45. The rate remained at about 56 per minute.

The following day, January 5, the patient was dazed but not delirious. She could answer questions intelligently, but was slow to recognize objects and people. The pulse remained very irregular and the heart sounds suggested myocardial weakness. Examination of the lungs and liver were negative. One mg. strophanthin was given at 9:50 a. m. At 2 p. m. fluid began to collect in the throat, which was expectorated with difficulty. Edema of the lungs developed and the patient died at 9:15 p. m., January 5, the heart remaining unchanged.

Electrocardiograms were made before, during and at frequent intervals after the second attack of unconsciousness. The records obtained on the day of admission (Fig. 1) show the normal cardiac mechanism, with complexes of the forms suggesting moderate left-sided predominance. They indicate no delay in the auriculoventricular conduction

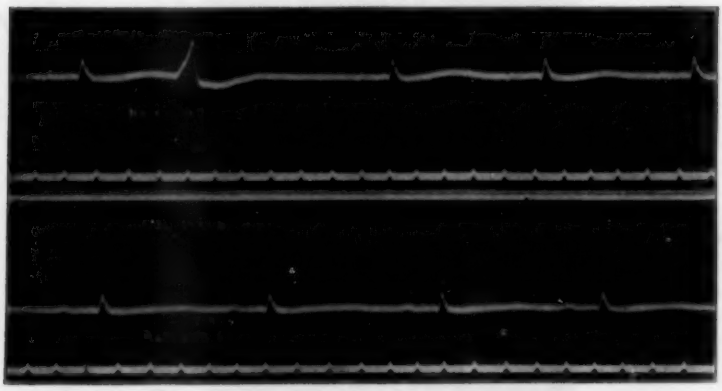

Fig. 4.—Curves obtained thirty minutes and seventy-two minutes, respectively, after the second period of ventricular fibrillation.

time. The heart rate was 100 per minute. The first record obtained on January 4, eight minutes before the second attack of unconsciousness, shows complexes nearly similar in form to those previously obtained, except that the A-V conduction time is now prolonged, the P-Q interval measuring 0.226 second (Fig. 2). The record obtained during the attack of unconsciousness at 2:48 p. m. is typical of ventricular fibrillation, as is shown by the curve which accompanies it, from a dog whose fibrillating ventricles were exposed by operative procedures (Fig. 3).

The next record was taken seventeen minutes later, at 3:05 p. m., and showed the heart beating regularly at a rate of 61.5 beats per minute.

At 3:18 the record (Fig. 4) shows the heart beating at a rate of

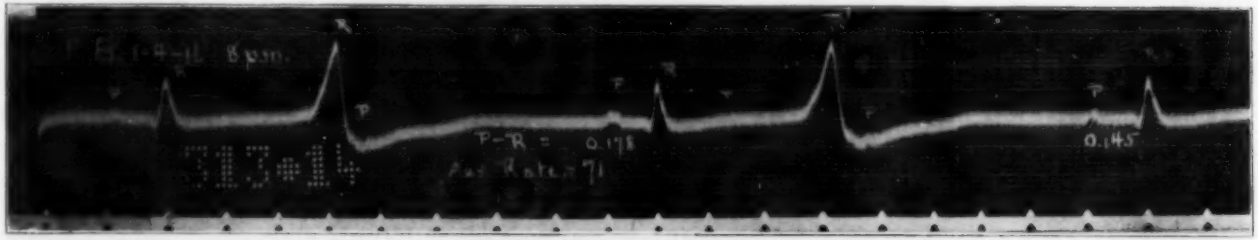

Figure 5-A

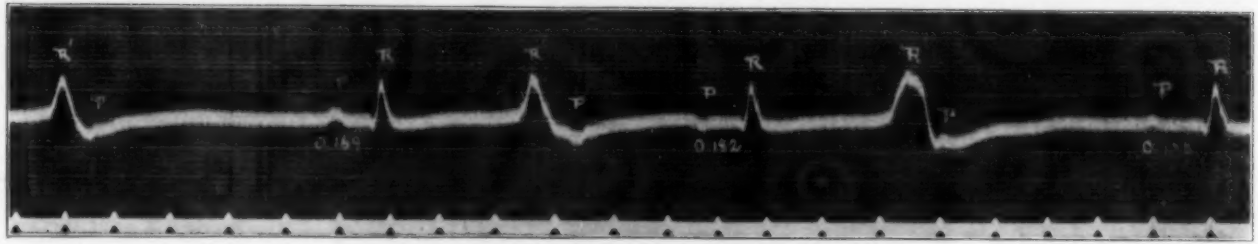

Figure 5-B

Fig. 5.—Obtained five hours after the period of ventricular fibrillation. Various abnormal complexes are seen.

57 beats per minute. The second lead is shown, and it is quite similar in form to that seen in the record obtained on the day of admission. Several unusual complexes occur, however, one of which is shown, a tall broad-based complex occurring prematurely. The P wave is inconspicuous and perhaps diphasic. Records obtained every few minutes after this one showed very little change. That obtained at 4 p. m. (Fig. 4) shows the heart beating regularly 53.6 beats per minute. The P waves have become well defined and no abnormal complexes appear. There is a distinct delay in the A-V conduction time. At 8 p. m. the

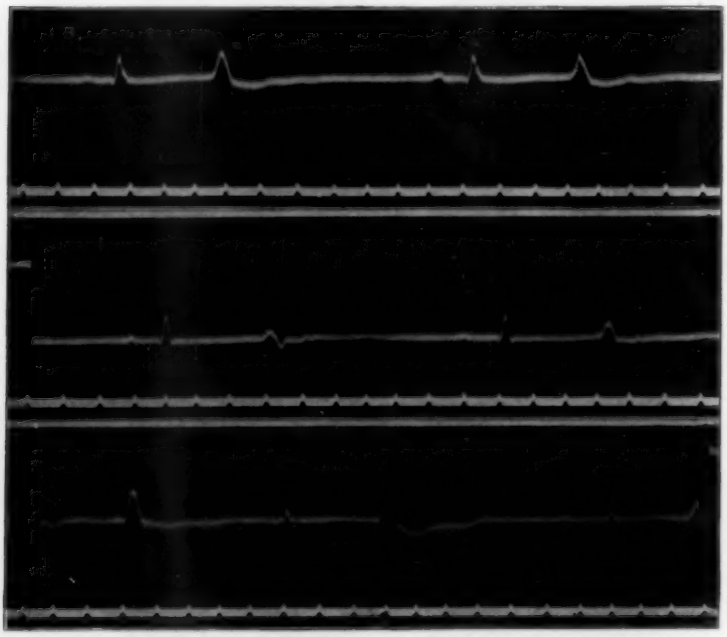

Fig. 6.—Three usual leads, twenty hours after the period of ventricular fibrillation, immediately before strophanthin was administered.

heart was beating irregularly (Fig. 5). Ectopic, premature ventricular contractions, yielding constantly varying complexes, were occurring after every normal beat. There was no delay in the A-V conduction time. The auricles were also beating irregularly, and at times the complexes yielded by premature contractions are unusual in form and vary from beat to beat.

No records were obtained at the time of the third period of unconsciousness and convulsive seizure.

At 9:45 a. m., on January 5, records were obtained immediately

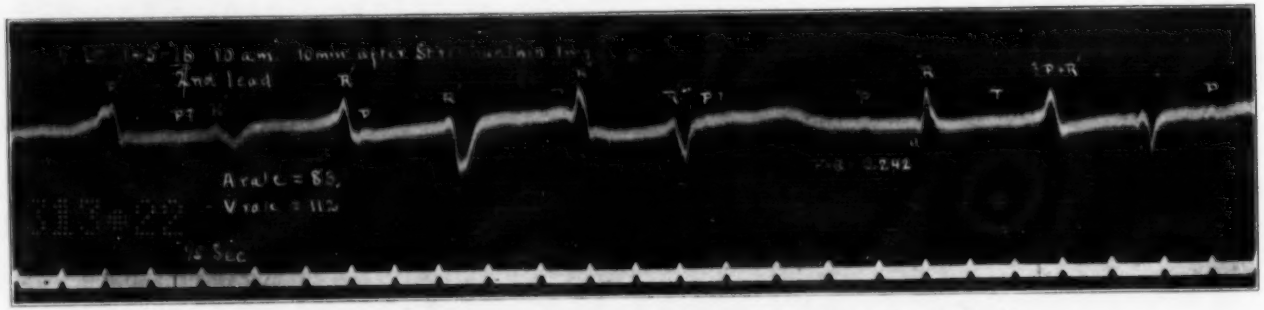

Fig. 7. — Record obtained immediately after the intravenous injection of strophanthin.

before the intravenous injection of 1 mg. of strophanthin (Fig. 6). The three leads are shown, and indicate that the cardiac activity was much as it had been the night before, abnormal complexes following all normal complexes. The form of the abnormal complexes show further changes, however.

The record obtained at 10 a. m., ten minutes after the strophanthin was given, shows many abnormal ventricular complexes following one another in rather rapid and irregular succession (Fig. 7). Only one sequential beat appears. This record indicates that numerous points in the ventricles were generating stimuli which spread over various paths through the ventricles. This record is of interest as regards the relation of the cardiac activity which it represents and fibrillation, as has been shown in experimental ventricular fibrillation, a point that will be referred to later.

The last record was obtained at 11:40 a. m., about nine hours before death, when the auricles were beating at a rate of 123 beats per minute (Fig. 8). Partial heart block and ectopic premature ventricular contractions occurred. The sequential beats yield complexes, however, quite similar to those obtained when the patient first entered the hospital, and, as far as this evidence goes, the occurrence of ventricular fibrillation produced no change which caused alterations in the sequential ventricular complexes.

Necropsy 587.—For the notes of the necropsy we are indebted to Dr. Opie.

Anatomic Diagnosis.—Bilateral carcinoma of the ovaries; chronic fibrous endocarditis of the mitral and aortic valves; hypertrophy of the left auricle and of the right auricle and ventricle; chronic passive congestion of the liver and spleen; edema of the lungs; bronchopneumonia; peritoneal effusion; chronic diffuse nephritis, with granular kidneys, of normal size; old pleural adhesions; arterial sclerosis; healed tuberculosis of the bronchial lymph nodes.

The heart weighs 290 gm. On the surface is a scant amount of fat which has a translucent, edematous appearance. The heart muscle is firm and red-brown in color. The thickness of the left ventricle is 16 mm. The left auricle has thickened walls measuring 2 mm. The endocardium has a gray, thickened appearance. The right ventricle is thickened, measuring 4 mm. The right auricle is also somewhat thickened. The mitral orifice measures 8 cm. The valve is thickened and the segments are fused together so that the valvular orifice is contracted. The valve segments are firm. The free edge is rounded and retracted. Just above the free edge there are several projecting vegetations. The chordae tendinae are thickened and shortened. The aortic orifice measures 6.7 cm. The semilunar folds are intact, but the free edges are slightly thickened and rounded, particularly in the neighborhood of the corpora arantii, from one of which there is a small projecting vegetation. The tricuspid orifice measures 11 cm., while the pulmonary orifice measures 7.7 cm. These valves are normal. The main branches of the coronary arteries are patent. An occasional elevated, yellowish area occurs in their lumen. The thoracic and abdominal aorta is thickly studded with elevated plaques, usually 0.5 to 1 cm. across, of yellowish color.

Microscopic examination of the heart muscle of both auricles and ventricles fails to reveal any distinctive lesion. The muscle fibers have a loose appearance as though separated by fluid, and there is moderate fragmentation. There is a slight general small round cell infiltration.

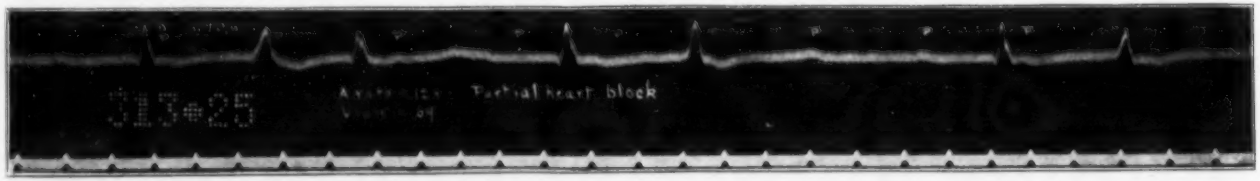

Fig 8.--Record obtained twenty-one hours after the period of ventricular fibrillation.

The necropsy throws no light on the cause of the ventricular fibrillation. It has been shown by Lewis[6] that obstruction to the blood flow through the coronary arteries in animals may result in ventricular fibrillation. The moderate grade of sclerosis of the coronaries in the case reported indicates, however, that the coronary blood supply was probably not materially interfered with, although the presence of vegetations on the mitral and aortic valves permits of the possibility of a coronary embolus which escaped detection at necropsy. The definite signs of cardiac insufficiency suggest the possibility of improper blood supply of the heart muscle as one of the results of this insufficiency. This may have been a factor in the production of the transient fibrillation of the ventricles.

Levy[7] has described an effect of light chloroform anesthesia which renders the ventricles especially prone to fibrillation. Ventricular fibrillation is then readily produced by the injection of epinephrin. The fibrillation produced by this method is always preceded by a stage of complex ventricular irregularities. Levy believes that fibrillation is a still more advanced and complex grade of these ventricular irregularities. They have been studied by means of electrocardiograms by Levy and Lewis,[8] who have shown that the ventricular irregularities preceding fibrillation consist in ectopic ventricular contractions arising from numerous foci. They consider this type of derangement of the heart beat as a transitional stage towards ventricular fibrillation, and have observed it also after recovery from fibrillation. Levy has called this condition, when ectopic beats arise from multiple foci in the ventricles, a state of potential fibrillation. The electrocardiogram shown in Figure 8, obtained immediately after the injection of strophanthin, is similar to those obtained by Levy and Lewis during this period of so-called potential fibrillation.

Much light has been thrown on the functional derangements of the heart which underlie fibrillation by the work of Mines[9] and of Garrey.[10] The former has studied the effect of successive induction shocks on the frog's heart, and found that under certain conditions which allow the muscle to respond to a rapid series of shocks, the refractory period of the muscle becomes shortened and the rate of propagation of the wave

6. Lewis: Mechanism of the Heart Beat, London, 1911, p. 160.

7. Levy: The Exciting Causes of Ventricular Fibrillation in Animals Under Chloroform Anesthesia, Heart, 1912-1913, **4**, 319. The Genesis of Ventricular Extrasystoles Under Chloroform: with Special Reference to Consecutive Ventricular Fibrillation, Heart, 1913-1914, **5**, 299.

8. Levy and Lewis: Heart Irregularities Resulting from the Inhalation of Low Percentages of Chloroform Vapor, and Their Relationship to Ventricular Fibrillation, Heart, 1911-1912, **3**, 99.

9. Mines: On Dynamic Equilibrium in the Heart, Jour. Physiol., 1913, **46**, 349.

10. Garrey: The Nature of Fibrillary Contraction of the Heart; Its Relation to Tissue Mass and Form, Am. Jour. Physiol., 1914, **33**, 397.

of excitation becomes slowed. Mines advanced an hypothesis explaining fibrillation based on these observations. He believed that when these changes occur a portion of the ventricular musculature goes very briefly into contraction, and the refractory period of this particular portion passes off before the impulse which travels slowly through the ventricular musculature again reaches it. Then this portion can go again into contraction. He suggests that such a circulating rhythm may constitute the condition known as ventricular fibrillation.

Garrey,[10] whose work was reported before that of Mines appeared, has carried the knowledge of the nature of fibrillation further, and by an ingenious experiment has been able to observe directly the passage of waves of muscular contraction through the heart muscle, which continued uninteruptedly to effect successive portions of the muscle, returning again and again to the same portion. His experiments form an adequate basis for his belief that fibrillary contractions of the heart muscle depend on the establishment within the musculature of multiple regions of block or reduced conductivity. The impulses thus blocked or delayed take abnormal and circuitous paths, and return to the same portion of the muscle after the refractory state has passed off, but while other portions are still refractory. The latter portions are subsequently involved in a similar manner, and the whole tissue mass is thus thrown into a continuous incoordinated contraction, which is not initiated or sustained by new impulses arising from any definite location.

The electrocardiograms of the patient here reported obtained after the attack of fibrillation indicate that there was present in the ventricles functional abnormalities which apparently predispose to fibrillation. The abnormal ventricular complexes, which vary greatly in form, indicate that cardiac impulses were arising in various points in the ventricles, and that these impulses were travelling through the ventricular musculature along abnormal paths. Many of these complexes are remarkably prolonged, especially in their initial phase, indicating that the impulses were passing through the musculature at an abnormally slow rate. These abnormalities are indicated most strikingly in the record obtained just after the intravenous injection of 1 mg. of strophanthin. The fact that the drug apparently brought the heart more definitely into the so-called state of potential fibrillation, seems worthy of emphasis in view of the fact that sudden death, perhaps from ventricular fibrillation has not infrequently occurred after the use of this drug. We have recently had one such experience, and a number of others have been reported to us verbally.

It seems probable that ventricular fibrillation is prone to occur in hearts in which there is a disturbance of the conduction of the impulse of the heart-beat through the ventricles. Such a disturbance would tend to produce the conditions which Mines and Garrey have described

as underlying fibrillation. A disturbance of intraventricular conduction may be detected by means of electrocardiograms, as has been recently pointed out by one of us,[11] and when such a disturbance is present it should be taken as a contraindication for the use of such drugs as chloroform, epinephrin and strophanthin, which predispose the heart to ventricular fibrillation. The case of sudden death which we observed after strophanthin yielded electrocardiograms suggesting such a disturbance, but unfortunately at that time we had not come to recognize their significance.

There is no direct indication as to why the heart in the case here reported should have recovered after ventricular fibrillation became established. The ventricles were relatively small, and would, therefore, be more likely to recover than those of a larger heart, as Garrey has shown that there is a definite relation between the size of the muscle mass involved and recovery. It is well known that recovery from ventricular fibrillation is not uncommon in smaller animals, as Gunn[12] has shown for at least one type of fibrillation in the rat. The larger the species or the larger the animal of a species the less likely is recovery from ventricular fibrillation to occur. This case is the first example of cardiac recovery from well established ventricular fibrillation that has been observed in man.

SUMMARY

A case is reported in which the patient showed marked cardiac insufficiency and had three attacks of cardiac syncope. During one of these attacks an electrocardiogram was obtained which is typical of ventricular fibrillation. The patient lived thirty hours after this syncopal attack, and numerous electrocardiograms were obtained during this time. One immediately after the intravenous injection of strophanthin showed a deranged cardiac mechanism similar to that observed experimentally by Levy and Lewis during the so-called state of potential fibrillation. The abnormal forms of ventricular complex which occurred frequently, were such as to indicate that there was a derangement of intraventricular conductivity. This may have been the prime factor in the production of the ventricular fibrillation. The occurrence of ventricular complexes indicative of derangement of intraventricular conductivity should be taken as contraindication for the use of drugs such as chloroform, epinephrin and strophanthin, which predispose the heart to ventricular fibrillation.

The foregoing case is the first example of cardiac recovery from well established ventricular fibrillation that has been observed in man

11. Robinson: The Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart, THE ARCHIVES INT. MED., 1916, **18**, 83.

12. Gunn: Ventricular Fibrillation in the Rat's Heart, Heart, 1913-1914, **5**, 1.

LOCALIZED AND INTERLOBAR PNEUMOTHORAX COMPLICATING PULMONARY TUBERCULOSIS *

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In our eagerness to discover tuberculous disease in the so-called incipient stage, we are apt to neglect the study of the symptoms and signs of the chronic forms of phthisis, though it is well known that the prognosis is quite favorable in the majority of the latter class of cases, even though they are designated as "advanced." Indeed, while caring for active cases of pulmonary phthisis we often attribute all the usual and unusual symptoms, the acute and subacute exacerbations and complications to one cause — the tubercle bacillus — and we forget that the lesions produced in the lungs by these bacilli are multifarious, and the prognosis in each is to be formulated by a study of the underlying changes noted in the individual patient. It is a matter of fact that in the vast majority of cases we can ascertain the exact pathologic, and often the etiologic, factors responsible for the sudden, or insidious, changes observed during the long and tedious course of the active period of the disease. Some of the complications which influence the prognosis are more or less easily discernible, as is the case with laryngeal, intestinal or peritoneal tuberculosis, pleurisy, spontaneous pneumothorax with complete collapse of the lung, etc.; but there are others which often escape detection, unless carefully watched for, all modern diagnostic aids being applied, and the findings properly interpreted.

Among the latter class of complications are the latent, partial, and interlobar forms of pneumothorax, which are quite frequent in cases of active phthisis, but only rarely recognized. Even when suspected, the localized form of pneumothorax is, in most cases, confused with large pulmonary excavations. Moreover, some are inclined to think that the differentiation between large pulmonary cavities and circumscribed pneumothorax is merely a pedantic diagnostic trick, at most of academic interest. "What difference does it make whether the cavity made out is in the lung or in the pleura? In either case the patient is doomed," said a physician to me recently. But in many cases it does make a great difference as regards the immediate and ultimate outlook. A patient with a localized pneumothorax may recover. In fact, it was this class of cases which gave the first impulse to treat certain phthisical

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* From the Tuberculosis Pavilion of the Montefiore Home and Hospital for Chronic Diseases.

patients by the induction of pneumothorax. On the other hand, a patient with a large pulmonary cavity, especially in the middle or lower lobe, has not a very good outlook for recovery. The differentiation between localized or interlobar pneumothorax and pulmonary excavation is therefore often of immense importance.

This was difficult in former times before we had the Roentgen rays at our disposal. But even now we are often unable to differentiate between the two conditions; after taking into consideration all the facts, the history, symptomatology and radiography, we are, at times, at a loss to state whether a given lesion is a pulmonary excavation or a localized pneumothorax. The following cases are published with a view to illustrating some of the forms of localized pneumothorax encountered by those who see many tuberculous patients, and to point out some of the difficulties in their differentiation.

Pneumothorax with complete collapse of the lung, when occurring in a tuberculous patient, is usually easily recognized by the clinical symptoms alone, excepting in the rare latent forms. The sudden onset, the acute distress, the dyspnea, prostration and collapse are unmistakable to the vigilant eye of the trained clinician. In most cases the physical signs are clear and unmistakable. But with the localized, especially the interlobar, forms of pneumothorax, things are different. In such cases but a small quantity of air can enter the pleural cavity because adhesions hold the two sheets of the pleura together, excepting over a small area, where it remains free and, on rupture of the visceral pleura, a gas pouch is formed. In many cases there are some symptoms, such as acute pain in the chest, dyspnea of greater or lesser severity, etc. But these symptoms are so often met with during the course of phthisis that they are usually attributed to the general condition, to acute pleurisy, etc., and the pleural gas pouch is not even suspected. Inasmuch as the physical signs are not always clear cut, exploration of the chest may not reveal the true condition; often a pulmonary cavity is diagnosed. Even a good roentgenogram may be inconclusive, as has been repeatedly the case in my experience.

Localized Pneumothorax Running an Acute and Fatal Course.—We often meet with cases of localized pneumothorax in which only a small portion of the lung is collapsed, with a symptomatology not unlike that of complete pneumothorax. It may prove fatal within a few days. The following is typical of this class of cases:

Case 1.—This patient, C. P., was a woman, aged 49 years. Her husband died from leukemia, her father from cancer, and a son from tuberculous pneumonia at the age of 23. She had typhus at 13, acute articular rheumatism at 21, and during the past eleven years has suffered from diabetes mellitus. Thirteen months before admission to the Montefiore Hospital, following exposure, she caught cold and began to cough, expectorate, etc. Soon fever, chills and night sweats made their appearance and she lost 70 pounds in weight

since the onset of her present illness. She had one copious pulmonary hemorrhage, and on several occasions expectorated blood-streaked sputum for several days in succession.

These symptoms continued unabated, yet she considered herself comparatively well until Feb. 7, 1917, when, without any ascertainable cause, she felt a severe and stabbing pain in the right infraclavicular region, and agonizing dyspnea. She suffered thus for three days, after which there was some improvement in her general condition, especially the dyspnea was relieved, but she grew weaker and weaker, and expired from asthenia February 17. No necropsy could be obtained.

Soon after the onset of the acute symptoms physical exploration of the chest revealed an air pouch in a circumscribed area over the upper third of the right chest. Instead of the bronchial breathing formerly audible over that area, we now elicited amphoric breathing of an exquisite type, and the whis-

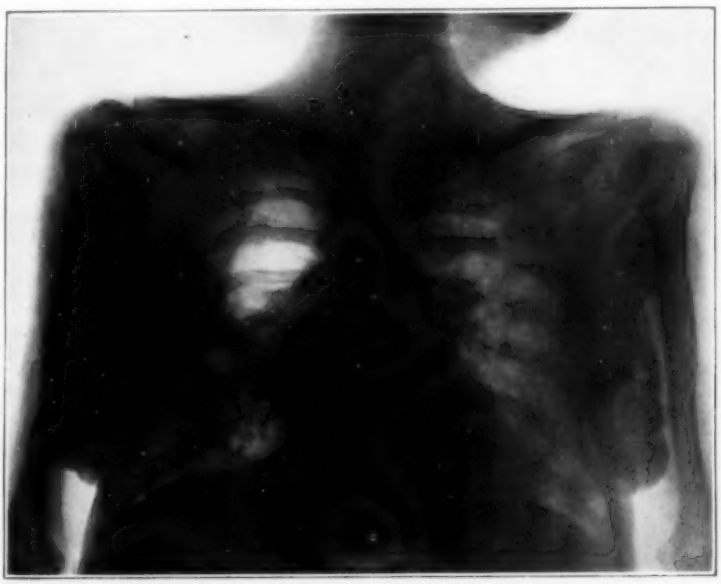

Fig. 1.—Localized pneumothorax of the upper part of the right pleura.

pered voice was clearly and distinctly transmitted directly into the ear; this last was especially audible in the axilla, a point which is to be borne in mind when attempting to diagnosticate such cases. The impaired note, elicited before the onset of the accident over the upper third of the right chest, remained the same, but now there was perceived a tympanitic overnote, and cracked-pot resonance was easily elicited. Two days later a metallic tinkle was clearly heard, and the bell sound was brought out vividly. The physical signs of a slight infiltration of the upper lobe of the left lung remained the same as they were before the onset of the acute symptoms, and the heart, liver, etc., remained in their normal position, which gave a clue that the pneumothorax was only partial.

The roentgenogram (Fig. 1) taken on the day following the onset of the acute symptoms, shows distinctly collapse of the upper third of the right lung—

a bright area lacking in lung markings. The lower border of this area shows a dark band suggestive of a dense, perhaps a fibrous, wall, often seen surrounding pulmonary excavations. But that we are not dealing with a large lung cavity is evident when we note that the intercostal spaces in the upper half of the right chest are wider than the corresponding ones of the left side of the chest. In large pulmonary cavities they are usually narrower than on the opposite side, though there are exceptions, as will be shown later. With a knowledge of the history of the patient, the sudden onset, the sudden appearance of the signs of excavation, the diagnosis is easy.

The difference between this type of pneumothorax and one in which the entire lung is collapsed, is mainly anatomic. The symptomatology, course and final outcome are about the same in both types. But not every case of localized pneumothorax pursues such an acute and fatal course. In many the symptoms are milder at the onset, are ameliorated within a few days, and the patient recovers sooner or later. While in many the underlying tuberculous process in the lungs is not at all altered in its course, in some the pneumothorax has a distinctly favorable influence on the phthisical process in the affected lung, and is a great factor in favoring recovery. The following cases illustrate the effects of localized pneumothorax in the manner indicated.

Latent Form of Partial Pneumothorax.—The pneumothorax may come on suddenly with more or less violent symptoms, but these soon abate and the patient feels well, the true lesion in the pleura passing unrecognized. The following case is a good example:

CASE 2.—S. D., a woman aged 30. Her family and personal history were negative, excepting that at the age of 18 she suffered from an attack of pneumonia and had ever since been troubled with "bronchitis"; she coughed, expectorated considerable quantities of sputum, etc. These symptoms came and passed periodically without materially impairing the patient's general health. Her present illness began about eight years before admission to the Montefiore Hospital with a moderate spell of hemoptysis which lasted a couple of days, and ever since she had been continuously coughing, expectorating mucopurulent sputum, had chills, fever and night sweats, felt tired afternoons and after slight exertion, lost weight and strength. An examination of her sputum revealed the presence of tubercle bacilli and she was advised to go to Colorado, where she remained three and a half years. She improved markedly in that mountainous region, but now and then suffered from acute or subacute exacerbations of her chest trouble, characterized by fever, cough, etc., and especially by recurrent attacks of hemoptysis. However, she got along fairly well until two years prior to this report when one day she was suddenly seized with a sharp pain in the upper part of the left chest and urgent dyspnea, soon followed by chills and fever. She remained bedridden for three weeks, but then improved and kept in fair health for two years, only occasionally suffering from acute or subacute exacerbations of her illness, but from which she on every occasion recovered within a few days, the process in the lungs remaining stationary or quiescent.

A physical and roentgenographic examination of the patient three and a half years after the accident occurred, revealed the presence of an air pouch in the middle of the left hemothorax, while the uppermost and lowermost parts of the viscus were bound down by pleural adhesions. Percussion yielded a dull note over the upper third and a flat note over the lower third, while in the middle third, especially in the axilla, there was elicited dulness with a

tympanitic overnote, and anteriorly over the second and third interspaces cracked-pot resonance was occasionally brought out. On auscultation very feeble breath sounds were heard over the lower third of the chest, bronchial breathing and large, moist, consonating râles in the upper third, and over the middle portion of the chest, both anteriorly and posteriorly, but most emphatically in the axilla, amphoric breath sounds and clear transmission of the whispered voice sounds were audible. Cough brought forth a distinct metallic echo over the last mentioned area, and the bell sound was pronounced on percussion with two coins and listening on the opposite side. It is important to mention that no adventitious sounds were heard in the portion of the chest where the amphoric phenomena were found, though all over the chest, especially anteriorly, large, moist, consonating râles were found. Another significant point is that the mediastinum was found markedly displaced to the left, the liver

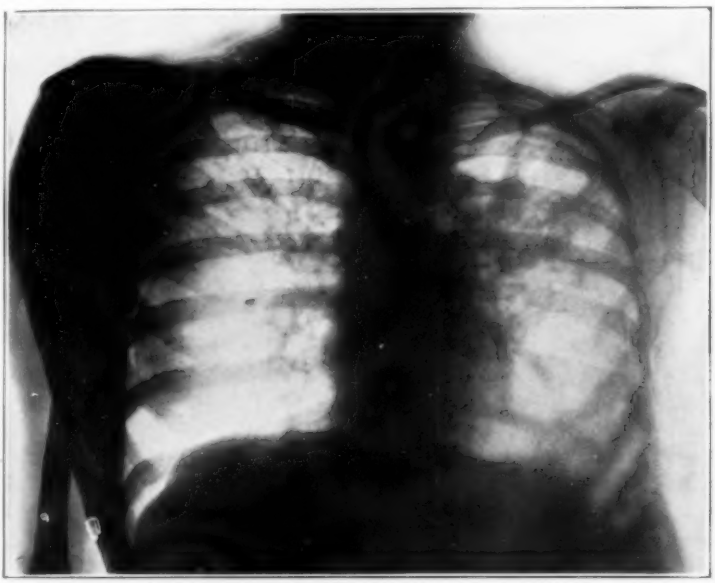

Fig. 2.—Localized pneumothorax of the upper part of the left pleura.

was enlarged and the spleen palpable. The right lung showed signs of emphysema—harsh, vesicular breath sounds, and over the apex bronchial breathing and subcrepitant râles were audible.

On admission, the question was raised whether the signs of excavation in the middle of the left chest were indicative of a pulmonary cavity, or of a localized, interlobar pneumothorax. In favor of a pulmonary cavity were considered the following points: There was seen clearly a retraction of the chest wall, and in pneumothorax we would expect that the intercostal spaces should be found widely separated, or obliterated on inspection of the external aspect of the chest. The cardiac displacement toward the affected side is characteristic of excava-

tion, while in pneumothorax, if any displacement had taken place, it would be expected that it should have been toward the unaffected side. On the other hand, in favor of a pneumothorax were the following points: The history of a sudden onset three years previously, the amphoric phenomena, the bell sound and the absence of râles over the area of tympanitic resonance. "Dry" cavities, with smooth walls over which exquisite amphoric breath sounds, and the bell sound are heard, are rare, and when they do occur they are usually located in the apex and not lower down in the chest, excepting as a terminal event in the course of phthisis, when they are no more "dry." The unusually loud transmission of the whispered voice, heard especially in the axilla, spoke very much in favor of a pneumothorax, because in excavation it is exceedingly rare in that location. The cardiac displacement to the left was explained by the fact that there were old pleural adhesions which contracted and pulled the mediastinum to the left and held it fast in that position. In fact, the enlarged, emphysematous lung in the right chest helped along in this direction. Considering that there was discovered a dull, almost flat note over the left lower lobe, and that there were indications that the left half of the diaphragm was pulled upward, it was clear that the lower part of the pleural cavity was obliterated.

Clinically, it was therefore decided that we were dealing with a localized pneumothorax in the upper part of the left chest. The roentgenogram, which was soon made, confirmed this view. It will be noted (Fig. 2) that the right lung is distinctly emphysematous, while in the apex there are signs of a slight infiltration. The lower half of the left chest shows signs of pleural thickening, the mediastinum is pulled toward the left and fixed in that position. Over the upper third of the left chest an air pouch is distinctly seen, while the collapsed upper lobe of the lung is pushed toward the mediastinum, and there is a sharp line of demarcation between it and the bright area devoid of lung markings. It appears that the pleural adhesions were so strong that they held back the ribs, so that in this case the intercostal spaces were not wider in the left chest than in the right, despite the pneumothorax, going hand in hand with the location of the mediastinum.

Case 3.—A. D., a man aged 35 years. His personal and family history were unimportant. He took sick two years prior to admission with cough, expectoration, fever, etc., but improved within one month and returned to work. But two months later the above symptoms reappeared, impairing his efficiency more acutely than the initial symptoms did. He coughed, had chills, fever, night sweats and lost weight. No dyspnea or palpitation were felt by the patient at that time. For nearly two years the disease pursued its course in the characteristic undulating fashion, the patient improving for a short period, to be soon undeceived by an acute exacerbation of the symptoms of phthisis. Three weeks before admission to the Montefiore Hospital, without any premonitory symptoms, and without any provocative or ascertainable cause, the patient felt a sharp stabbing pain in the left chest, "in the heart," as he described it,

urgent dyspnea, palpitation, cyanosis, etc. Soon his temperature rose to a high level, but within five days the fever abated, the dyspnea ameliorated and his general condition improved, so that when admitted, three weeks after the onset of the acute symptoms, he felt quite well. The dyspnea was mild, and pronounced only after exertion, the temperature quite normal; no night sweats; he had a good appetite and was regaining his lost weight.

Physical exploration of the chest revealed signs of a tuberculous lesion in the right apex with a small cavity in the supraclavicular region, while the lower two thirds of the right lung showed indications of emphysema. The entire left side of the chest was dull on percussion, the diaphragm high and immobile; above the second rib and below the fifth the note elicited was almost flat. From the second to the fifth rib anteriorly, and more so on that level in the axilla, the note was also impaired, but a tympanitic overnote was distinctly made out. Over the same area the breath sounds were feeble, but the

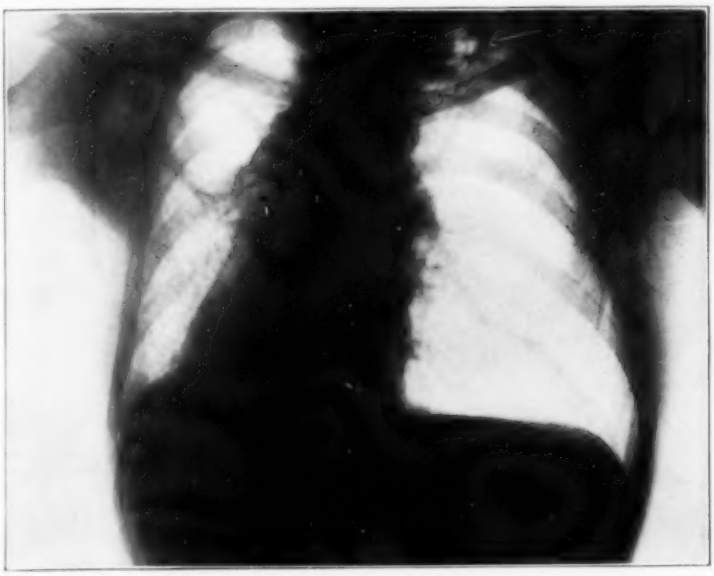

Fig. 3.—Large cavity in right apex; collapsed upper lobe of the left lung.

whispered voice sounds were transmitted clearly and distinctly. A few râles were at times heard over that area, and a metallic tinkle was at times audible. The coin sound was positive. The heart was found displaced to the left.

Here again the question arose at the first examination whether we were dealing with a large excavation of the upper third of the left lung, or with a localized pneumothorax. The roentgenogram gave similar doubtful criteria. It will be noted (Fig. 3) that the cavity in the right apex is distinctly shown above the clavicle, as is the emphysema in the entire right lung below the clavicle. The cause of the dulness over the lowermost part of the left chest is also revealed in the

roentgenogram — thickened pleura and elevated diaphragm. But the clear area, lacking in lung markings, above the third rib, is not easily interpreted. The lower limit of this area, deeply and distinctly demarcated by a thick shadow, would suggest the wall of a cavity; the thick dark line crossing the cavity may represent a fibrous or a vascular band, such bands being not uncommonly seen in extensive pulmonary excavations. The pleuropericardial adhesions and the displacement of the mediastinum and diaphragm are also in favor of the lesion being a pulmonary cavity. But, on the other hand, the absence of a shadow above the clavicle, or of indications of a wall of a cavity surrounding it in its upper and outer limits, speak in favor of a pneumothorax, though we will show later that this is not a very reliable criterion. It appears, however, that the bright area above the clavicle is expanded in its transverse diameter, which is never seen in an excavation, and is characteristic of a pneumothorax, except when the dome of the lung is bound down by adhesions of the pleura. This, taken in connection with the history of the case, as well as the physical signs, especially the coin sound, the metallic tinkle and the râles over that area, and also the width of the intercostal spaces, speaks in favor of a pneumothorax. While some of these signs may exceptionally be found over large excavations, the very clear transmission of the whispered voice high up in the arm pit is against an excavation.

Latent Localized Pneumothorax Simulating a Cavity.—

Case 4.—The case of M. I. shows more conclusive evidence as to the true condition in the chest. He was 43 years old and gave a family and personal history having no bearing on his present illness, which began three years prior to admission with pain in the right chest anteriorly, cough and expectoration, but, according to the patient, neither fever nor night sweats were noted at that period. He continued in this condition of semi-invalidism until eight months before admission to the Montefiore Hospital, when he began to feel short of breath and suffered from cardiac palpitation, especially after mild exertion, but he gave no history of any acute pains in the chest. At that time, he said he had some fever, but this abated within about ten days. Since then his cough is milder, his temperature practically normal and he expectorates very little. His general condition, excepting dyspnea and palpitation, is good; in fact he has gained 14 pounds in weight.

Physical examination of his chest showed signs of emphysema in the left lung, with a slight infiltration of the apex, and moist, coarse râles scattered all over that side. The percussion note elicited over the lower third of the right chest was flat, and dull all over the upper two thirds excepting where tympany was elicited. Wintrich's sign was also elicited in that plane. On auscultation there was found a circumscribed area of amphoric breathing and whispered pectoriloquy over the right supraspinous fossa near the spine, and over the right axillary region, extending anteriorly as far as the right margin of the sternum and posteriorly to the inner margin of the scapula, exquisite amphoric breath sounds and clear whispered pectoriloquy were audible. At times a metallic tinkle was heard, but râles were never heard over any part of the right side of the chest. The coin sound was well produced over the area with amphoric breath sounds. The physical examination thus showed a small cavity in the apex, and a localized pneumothorax over the middle third of the right lung, probably of the interlobar variety.

The roentgenogram confirmed these findings. The clear area, free from lung markings, is distinctly seen (Fig. 4) in the right side of the chest, and the collapsed middle lobe of the lung near the mediastinum cannot be taken for aught else than indications of pneumothorax. The wide intercostal spaces would be inconceivable if there were a pulmonary cavity in that place. On the other hand, we find here that the heart and trachea are displaced toward the right, which would speak against a pneumothorax. In fact, the left lung of the patient is emphysematous and enlarged so that it may have been the *vis a tergo*

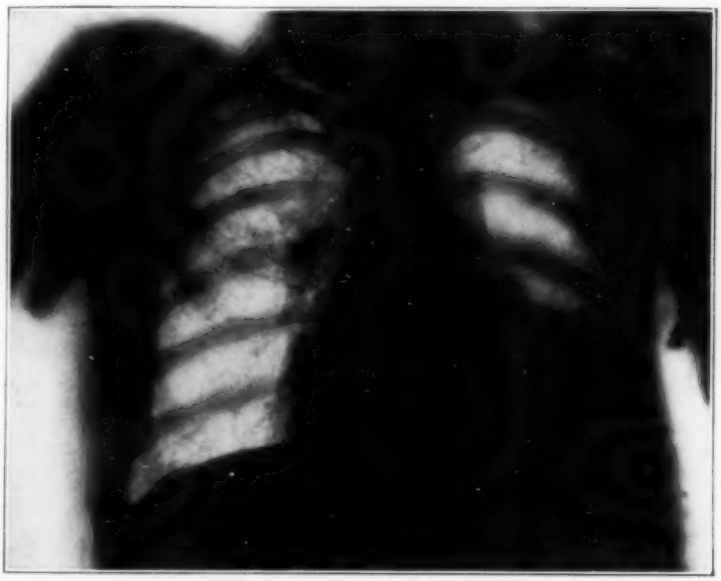

Fig. 4.—Localized pneumothorax of the right upper and middle lobes. Note the wide separation of the ribs over the airless area.

assisting in pushing it to the right, where it had been held fast by pleural adhesions.

There are other features in this case, however, which speak in favor of an interlobar pneumothorax. The fact that since the onset of the dyspnea and palpitation, combined with the signs of excavation over the middle of the right lung, the patient's general condition improved — he had no fever, coughed but little, hardly expectorated and has gained materially in weight — are important points. Patients with large excavations in the lower or middle lobes of the lung are not doing well; pulmonary excavations in these regions are usually ter-

minal phenomena in phthisis, as is well known to those who see many tuberculous patients in the advanced stages of the disease. The reason is probably that basal cavities do not drain well, and those in the middle lobe cannot drain as well as those in the upper lobes.

In this case, while there was no history of an acute onset with pain, prostration, etc., still the patient said that about eight months previous to admission he suddenly began to feel short winded, with cardiac palpitation. The latency of a localized pneumothorax may, however, be even more accentuated, and the history entirely negative, as can be seen from Case 5.

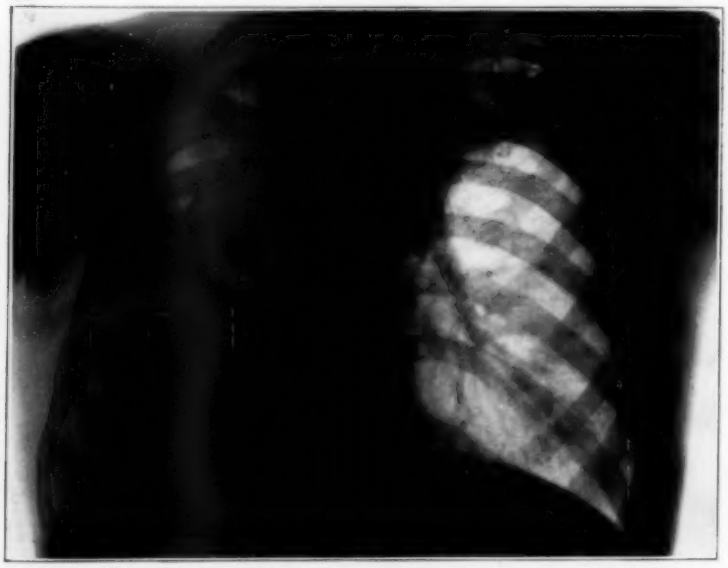

Fig. 5.—Localized pneumothorax of the right upper lobe; dextrocardia.

Case 5.—S. S. was a man aged 21 years. His illness dated back two years, when he began to cough, lose flesh, have fever, night sweats, etc. Tuberculosis was soon diagnosticated and treatment instituted. He got along fairly well, improving for a few months and suffering now and then from acute or subacute exacerbations, manifested by fever, night sweats, excessive cough and expectoration, etc. He had no acute symptoms, such as pain in the chest or prostration, at any time, but for many months had been suffering from dyspnea, which came on gradually and was becoming more and more pronounced. On admission, Feb. 16, 1917, we found that he was afebrile; his cough was quite mild, and during a rest of two months in the hospital he gained 10 pounds in weight.

Physical exploration of the chest showed almost complete dextrocardia and the liver pulled upward. There were also found signs of an infiltration of the left apex. The chest wall of the right side was found retracted and almost

immobile, flat on percussion of the lower third, the upper two thirds dull. There were no cracked-pot resonance, or Wintrich's or Gerhardt's signs. In the axillary region and extending anteriorly to the mamillary line and posteriorly to the angle of the scapula was found an area of exquisite amphoric breathing with a clear transmission of the whispered voice; this pectoriloquy was audible high up in the arm-pit. Frequently a metallic tinkle was heard, but the bell sound was negative. There were no râles anywhere.

A diagnosis of localized pneumothorax was made on these findings, despite the fact that there was cardiac displacement toward the side with the lesion, the negative history of an acute onset and the retraction of the chest wall. The roentgenogram confirmed the diagnosis. As will be seen from Figure 5, the pneumothorax is quite clear and distinct in the right side. The thick pleura, the elevated diaphragm and liver and the dextrocardia are also seen in the roentgenogram.

Pulmonary Cavity.—The following case is detailed here with a view to showing that in the average case with a large pulmonary excavation, the diagnosis is simple with or without roentgenographic examination.

Case 6.—S. K., a woman aged 22 years, began to cough two years before admission to the hospital, and two months later suffered from an attack of pleurisy in the left chest. She lost in weight persistently during the succeeding six months, had fever, night sweats and annoying cardiac palpitation. During the previous year she has been improving, the palpitation had subsided, her fever abated, and for the previous eight months her temperature had been practically normal, except for a few days now and then, when it rose to 100 F. She coughed but little and brought up very little sputum. Her general condition was so good that she was never confined to bed.

A physical examination of her chest showed a fairly healthy lung in the right side of the chest, except for some indications of emphysema and inconclusive signs of an infiltration of the apex, especially posteriorly. Over the upper third of the left chest signs of a large excavation were elicited. The percussion note was dull above the fourth rib anteriorly and to the sixth thoracic spine posteriorly, and again for a few inches at the base there was found a tympanitic overnote over a circumscribed area between the clavicle and the third interspace. Cracked-pot resonance and Wintrich's sign were also brought out over this spot. Cavernous breath sounds, large moist consonating râles, which we are wont to call "cavernous râles," and exaggeration of the transmission of the whispered voice were heard on auscultation over this area. Gerhardt's sign was not found. The mediastinum was displaced to the left and upward, while on inspection the left chest showed distinct retraction of the upper half anteriorly.

Because the whispered voice sound was distinctly audible only between the clavicle and the third interspace, and not in the axilla or posteriorly, and because of the large moist râles and retraction of the anterior chest wall, a cavity was considered the most likely change in the left lung. A roentgenogram confirmed these conclusions. It will be noted (Fig. 6) that the intercostal spaces over the upper third of the left chest are narrower than the corresponding spaces in the right half of the chest; there is no clear and bright area lacking in lung markings and shadows. The somewhat bright, circumscribed area above the third rib is surrounded by a dense shadow, indicative of a thick, probably fibrous or caseated wall.

That these distinctions are not always conclusive is well known to those who have opportunities to verify their clinical findings, interpretations of physical exploration of the chest and roentgenograms by necropsies. Thus, I have seen a case in which the physical signs, the history and the symptomatology were of a localized pneumothorax

over the right upper lobe, but the roentgenogram showed an infiltrated and caseated lobe in that location. Further investigation showed that while there were thick adhesions of the posterior aspect of the pleura, the two sheets remained free anteriorly over a limited area, and there a pneumothorax occurred, forming an air pouch which could be made out clinically, but the collapsed lung, pushed toward the posterior wall of the thorax, acted as a screen, and the roentgenogram failed to show the presence of a pneumothorax. Only careful fluoroscopy can reveal such a localized pneumothorax. On the other hand, a large cavity may often be easily diagnosed by physical signs, but the roentgenogram

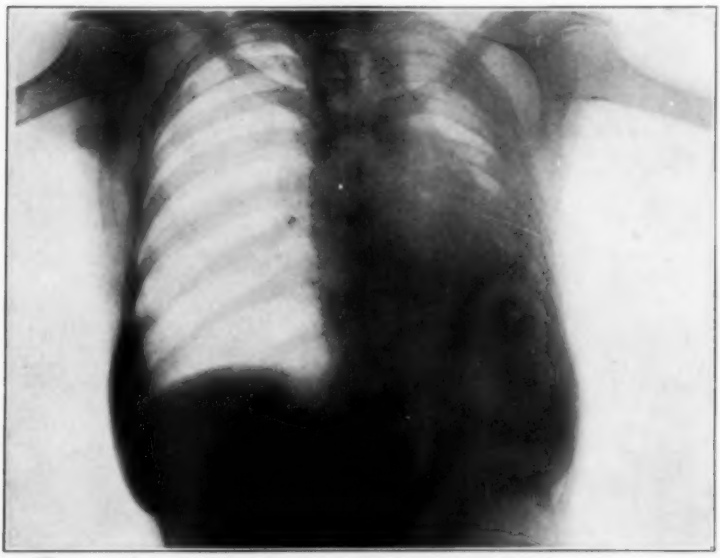

Fig. 6.—Large cavity in upper lobe of the left lung; sinistracardia. Note the narrow intercostal spaces over the site of the cavity.

shows distinctly and incontrovertibly a pneumothorax. In such cases the clinician is at a loss, and a necropsy alone can clear up the diagnosis. The following cases illustrate the points just raised.

Case 7.—E. M., a woman aged 21 years, was taken ill eighteen months before admission to the Montefiore Hospital, with high fever, cough and expectoration. The disease was progressive in character, and after admission to a sanatorium several attempts were made to create artificially a pneumothorax for therapeutic purposes. But because of pleural adhesions all attempts proved futile, no gas could be introduced; roentgenographic examinations have shown that no gas was introduced into the pleural cavity. In January, 1917, she began to have a high fever, had chills and profuse night sweats, and physical exploration of the chest showed that the process had extended so as

extensively to implicate both lungs. Finally, symptoms of tuberculous peritonitis developed, purpura hemorrhagica made its appearance over the front of the chest and abdomen, and she succumbed March 20, 1917.

A physical exploration of the chest a few days before the patient died showed signs of large excavations in the upper parts of both lungs anteriorly and posteriorly. The cavity in the right lung was apparently larger than that in the left. Above the third rib anteriorly impaired resonance was found, but over a circumscribed area between the second and fourth ribs near the sternum a distinctly tympanitic note was elicited; cracked-pot resonance and Wintrich's sign were also found in that location. Cavernous breathing, coarse, consonating, moist râles, and distinct transmission of the whispered voice were found over the same area of the right chest anteriorly, also posteriorly in the upper third of the interscapular space, over the left suprascapular space, and anteriorly over the first left interspace. The whispered voice

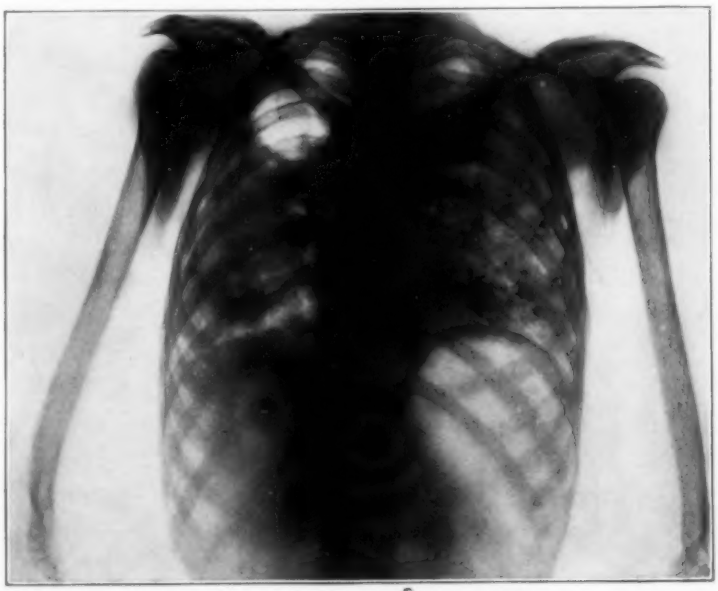

Fig. 7.—Roentgenogram showing distinct signs of a localized pneumothorax in the upper part of the right chest. Clinical signs were in favor of a cavity. Necropsy confirmed the clinical findings. See Figure 8.

was not audible in either of the axillae. The coin sound could not be elicited. Multiple excavations of both lungs, especially the right, were diagnosticated.

A postmortem roentgenogram, taken two days after the physical examination, disclosed, to our great surprise, signs of a localized pneumothorax in the right chest above the third rib (Fig. 7). The bright area in that location is very suggestive of a pleural air pouch, considering that above the clavicle there are no signs of any normal or diseased lung tissue, and the width of the intercostal spaces is about the same as of those on the opposite side. On the other hand, the deep, dark shadow demarkating the lower limits of the excavation is rather suggestive of a thick wall surrounding a pulmonary excavation—caseated lung tissue, in fact. The excavation in the left apex is

distinctly shown. Any one examining this plate, however, would unhesitatingly pronounce the lesion in the uppermost part of the right chest a pneumothorax.

A necropsy, made by Dr. B. S. Kline, showed that the clinical history and the findings on physical exploration were more trustworthy in this case

Fig. 8.—Right lung of patient, Case 7. Note the large cavity in apex and the thick pleura.

than roentgenography. As will be seen from the reproduction of a photograph of the right lung (Fig. 8), the visceral and parietal pleurae were densely adherent and could not have been the seat of a pneumothorax, especially over the upper lobe, where the roentgenogram showed clearly the existence of such a condi-

tion. Within the upper lobe was found a large cavity, 7 cm. in diameter, containing cheesy matter and traversed by bridges of connective tissue. The small cavities, discovered clinically in the upper lobe of the left lung, were also found when the lung was cut into.

Another case in which the divergence between the findings on physical diagnosis and on roentgenography was strikingly in favor of the former, as proved by necropsy, is the following:

Case 8.—S. E., a man aged 49, gave a family and past history which have no bearings on his present disease. For twenty-five years he had been coughing and expectorating, especially during the morning hours, but his general health had not suffered as a result of these symptoms, and he kept at work without

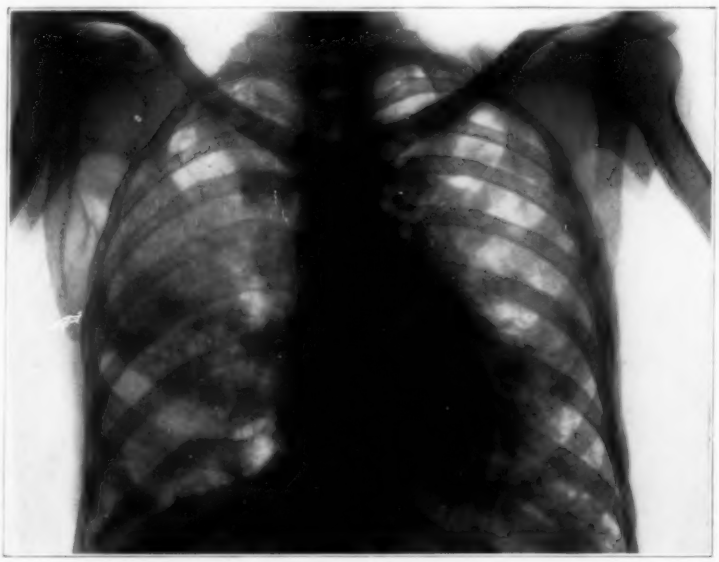

Fig. 9.—Roentgenographic indications of a localized pneumothorax in the upper part of the left chest. Clinical findings favored the diagnosis of a cavity.

any notable interruptions; nor had he suffered from constitutional symptoms, such as fever, loss of weight, etc. He said that about one year before admission to the hospital he caught a severe cold and began to cough more severely than formerly. The cough was unproductive, but he lost weight progressively. Fever and night sweats made their appearance and an examination of his sputum revealed the presence of tubercle bacilli. In search of health he went to several sanatoriums and health resorts, but without avail; the disease kept on progressing. On admission to the Montefiore Hospital we found that he suffered from moderate intermittent fever, recurrent chills, night sweats, etc., and the cough and expectoration were very troublesome. Repeated inquiries did not elicit any history of a sudden change in his condition, nor of any pain in the chest which might be interpreted as due to rupture of the pleura. He died from asthenia after remaining in the hospital five weeks.

A physical examination of the chest showed that there were signs of a slight infiltration of the right apex. The main lesion, however, was found in the left lung. Posteriorly there was found a circumscribed area of cavernous breathing and whispered pectoriloquy over the left supraspinous fossa, indicating a cavity in that location. Anteriorly on the left side, the upper half of the chest was dull, but "boxy" over a circumscribed area between the second and fourth ribs, especially toward the axilla. Traube's space was dull on percussion, indicating retraction of the lung with elevation of the diaphragm, especially since in that place there was also a friction sound and feeble breath sounds. Over the area with dull tympany, or boxy resonance, distinct amphoric breath sounds were heard, but no whispered pectoriloquy was elicited, which would suggest that the excavation was apparently located posteriorly, where the signs were more conclusive. In fact, no cracked-pot resonance, Gerhardt's or Wintrich's signs were found. It was, however, a striking phenomenon that the coin test was positive, which would speak in favor of a pneumothorax, though we have, on rare occasions, heard it in chests with pulmonary excavations. A diagnosis of a large excavation in the left upper lobe and part of the top of the middle lobe was made. The presence of the coin sound suggested that further investigation might bring forth some surprise.

The roentgenogram made after the physical examination showed some signs suggestive of a localized pneumothorax (Fig. 9) above the third rib in the left side of the chest. Indeed, the roentgenographer marked it as such.

A necropsy, performed by Dr. B. S. Kline, showed that roentgenography in this case was again more likely to err than physical diagnosis. There was no evidence of a pneumothorax. Indeed, it would have been impossible for air to enter the pleural cavity because the two sheets of the pleura were tightly adherent, especially over the upper third of the lung. Both lobes of the left lung were voluminous and adherent at the interlobar fissure; the upper lobe was almost entirely converted into connective tissue, but on section there was found a large cavity, about 15 by 11 cm. The excavation was filled with cheesy matter and it was traversed by bridges of connective tissue. Posteriorly the wall of the cavity was made up of the thickened pleural sheets, while anteriorly and laterally it was encapsulated by a thick and firm layer of gray fibrous tissue. Several branches of the bronchi terminated within the cavity (Fig. 10).

The reason why the amphoric phenomena were not distinct on the anterior chest wall over this cavity is perhaps explained by the large amount of caseous matter within the excavation, and also, in all probability, the communicating bronchi were obstructed at the time of the examination. But what is most noteworthy is the observation of an airless area, devoid of lung markings, simulating a pneumothorax on the roentgenogram (Fig. 9). The following is a point worthy of consideration by roentgenologists: A large excavation without areas of calcification may permit the Roentgen rays to pass and produce a bright spot on the plate. In other words, not all circumscribed bright areas on plates are due to pneumothorax, even when they do not show any dense, dark surrounding walls, as was the case with this chest.

Another important point is that over this cavity we found the coin, or bell, sound. This sign has been considered pathognomonic of pneumothorax, and it has been said that over large air-filled cavities having smooth walls, the clear, ringing bell-like sound may be heard. In this case the walls of the cavity were anything but smooth, and the cavity

was filled with secretions, so that the conditions for reverberation of sound were not favorable, yet the phenomenon was distinctly audible on several occasions.

These cases constitute drastic illustrations of the fact, observed by

Fig. 10.—Lung of patient, Case 8. Thick pleura and excavation.

many clinicians, that while roentgenography is an indispensible aid in diagnosis and in differentiating pathologic changes in the thoracic viscera, yet it is apt to prove misleading. In fact, I have frequently been confused by interpretations of Roentgen-ray reports when they were

in conflict with the clinical findings, and feel that if only one method were available, I would choose physical diagnosis in preference to roentgenography. Especially is this true of the diagnosis of localized pneumothorax. It is frequently difficult to differentiate between a large cavity and a pneumothorax. A thickened pleura, which is frequent in these cases, is apt to screen the lesion in a peculiar fashion. It is often not at all shown on the roentgenogram, unless it contains calcified tissue, which is uncommon; while caseated lung tissue invariably casts a deep shadow. When there is a thick pleura over the main lesion, and the caseated parenchyma has been thrown off by softening, the roentgenogram may show a circumscribed area lacking in lung markings; in fact, as bright as if there were a localized pneumothorax. It has been suggested that in such cases it is instructive to take several plates under various conditions. In cavitary cases we may find that after a restful night's sleep, brought about by an opiate if necessary, the bright area disappears, and a dark shadow, surrounded by a thick and darker margin, has appeared, owing to the large amount of secretions accumulated during the night. Clearing the cavity, especially by the postural methods — placing the patient in certain positions — may again be instrumental in producing the bright circumscribed area on the roentgenogram. Such changes in the observed phenomena may be conclusive, because a localized or interlobar pneumothorax will always show the same appearance on the skiagram. Of course, this is a rather tedious and costly procedure and cannot be done in every doubtful case.

DISCUSSION

Localized and interlobar pneumothorax are frequent in cases of chronic phthisis. They are often overlooked and confused with large pulmonary excavations because the physical signs, symptoms and also the roentgenograms are at times similar in both conditions and require careful discrimination for differentiation. While this paper was being prepared, we analyzed critically in the Montefiore Hospital the cases having large cavities, and during two months seven patients were discovered having localized pneumothorax, though in some of these cases it was thought that we were dealing with pulmonary excavations. In some we thus found a ready explanation why the patients got along very well, though apparently they had large cavities in their lungs. I have no doubt that in other hospitals harboring tuberculous patients in the advanced stages of the disease the number with localized and interlobar pneumothorax is not less than in our institution.

Considering that the prognosis is much better, as a rule, in cases with localized pneumothorax than in those with large cavities, it is important to differentiate between these two conditions. Occasionally

it is decided to induce a pneumothorax in one pleura for therapeutic purposes despite the fact that in the opposite side there are signs of excavation. It is then important to make sure that the "cavity" is not in reality a localized pneumothorax. This, in fact, has happened in one of my cases. In many cases the roentgenogram will reveal the true condition, even when clinically a pneumothorax was not suspected. In fact, since the introduction of the Roentgen ray as a diagnostic aid, localized and interlobar pneumothorax are more often found than formerly. But the roentgenographic findings are not always conclusive, and frequently they may only be correctly interpreted after they are considered in connection with the history of the patient and the findings on physical exploration of the chest.

The history of the onset is important. A cavity of large dimensions does not occur suddenly, while signs of a localized pneumothorax appear within a few minutes. If we know the condition of the chest of the patient, the sudden appearance of signs of excavation, such as tympany, amphoric breathing and pectoriloquy over a circumscribed area, should suggest pneumothorax. In most patients we find that there was a sudden change for the worse, even in patients who have been doing well. A sharp, stabbing pain in one side of the chest is felt, followed by dyspnea, cyanosis, prostration of variable degree, etc. Some patients succumb to these symptoms within a few days, or one or two weeks, as is illustrated by the first case here reported. Others last for several weeks or months, bed-ridden and in agony, finally succumbing to asthenia, tuberculous bronchopneumonia, etc. But in many patients the pneumothorax is effective in improving the general condition soon after the acute symptoms subside. The pain disappears, the dyspnea is ameliorated, though they may remain more or less short-winded even on mild exertion. However, at times we meet with patients in whom the symptoms which tormented them for months, such as cough, expectoration, fever, nightsweats, anorexia, emaciation, etc., are all more or less ameliorated after the onset of the pneumothorax. Because of the abatement or disappearance of the symptoms of toxemia, the patient gains in weight and strength, and feels quite well, though physical examination reveals the presence of a large air-filled cavity in the pleura. Cases 2 and 3 previously reported are examples of this class.

The sudden appearance of pain in the chest, and especially of dyspnea in a tuberculous patient, if not found to be due to pleurisy or myocarditis, should urge a thorough physical exploration of the chest. The following points may serve in attempts at differentiation from pulmonary excavation: In localized pneumothorax the cavity is, as a rule, "dry," no adventitious sounds are audible; while large excava-

tions usually show large, moist, consonating râles and gurgles. A large "dry" cavity, especially when extending to the axilla, should not be accepted as such without careful investigation. The breath sounds in pneumothorax are distinctly amphoric or metallic; such exquisite metallic sounds are exceedingly rare in cavities. But it must also be borne in mind that in the former there may be feeble, or entire absence of, breath sounds, which is also true of cavities, especially when the communicating bronchus is plugged by secretions or swollen, or when it is altogether filled with secretions. In cavities we at times perceive metamorphosing breathing, which is never heard in pneumothorax. On the other hand, in some cases of pneumothorax a metallic tinkle is heard; in cavities, very rarely.

Of great diagnostic importance in the differentiation of these two conditions is auscultation of the whispered voice sounds. In cavities bronchophony is the rule and whispered pectoriloquy is frequently absent, while in localized pneumothorax the latter is commonly present and is strikingly pronounced, clear and articulate, usually perceived as if spoken directly into the stethoscope, a phenomenon exceedingly rare in pulmonary excavation, in which only the spoken voice is transmitted. The whispered echo is also more frequently heard in pneumothorax. Moreover, in localized pneumothorax, especially in the interlobar variety, whispered pectoriloquy is distinctly, or exclusively, heard high up in the axilla, which is very rare in cases with excavations. This is a diagnostic point which is very reliable, and it is rather curious that it has not heretofore been emphasized, or even mentioned. A sharp echo, audible when the patient coughs, may be heard in both conditions, but its ringing quality is more pronounced, as a rule, in pneumothorax.

Percussion may give some criteria for diagnosis. Over cavities the note elicited is dull, and only in very emaciated patients, with excavations located superficially, do we find tympany over a circumscribed area. In pneumothorax tympany is more frequently elicited, at least a tympanitic overnote, and in the interlobar variety it is very clear high up in the arm pit. Cracked-pot resonance may be elicited in both conditions, though more frequently in cavities; the same is true of Wintrich's sign. The coin test is of value, when positive; it is exceedingly rare in cases with cavities, while over localized pneumothorax it is at times found. In some it is found only in certain positions; it may be present on one day and absent on another.

On inspection of the chest we may get some hints as to the intrathoracic lesion. Retraction of the chest wall is characteristic of large cavities, while bulging may be found, though rarely, in cases of localized pneumothorax. Recalling that in nearly all chronic cases there are pleural adhesions of greater or lesser density, otherwise the pneumo-

thorax would be complete, we have a reason why retraction and flattening of the chest wall over the site of the air pouch is at times found with a localized pneumothorax, and the intercostal spaces are not always wider than their mates on the opposite side. But when found, separation of the intercostal spaces is pathognomonic of a localized pneumothorax, because it is only rarely seen in cavitary cases. This is usually best observed on the roentgenogram. It is noteworthy that in Case 7 reported here the ribs are widely separated, though the necropsy showed a cavity (Fig. 7).

The location of the mediastinal organs gives no reliable clue as to the true lesion. They are almost invariably displaced toward the side affected with a large cavity. In many cases, when the heart has thus been displaced, a small localized pneumothorax subsequently formed in the same side, may not be effective in pushing it back to the opposite side. When the pneumothorax is more extensive and the adhesions not old and dense, the heart may be displaced. But in many cases, as we have seen, the heart remains in its normal place, or is found displaced toward the affected side, just as in cases with excavations. The reason has just been indicated — old adhesions hold it fast in the place it was before the rupture of the pleura occurred.

The roentgenographic findings are invaluable in most doubtful cases. A bright, circumscribed area, lacking in lung markings, when not surrounded by a thick, dark shadow, is pathognomonic of a localized pneumothorax. But at times even this is deceptive. The air pouch may be located anteriorly, while posteriorly is adherent lung tissue which screens it, and no bright area appears on the roentgenogram, as I have seen in some cases. On the other hand, the walls of the pulmonary cavity may not cast a shadow on the roentgenogram, and as a result we may find on the plate a picture clearly showing a pneumothorax, while the real lesion is a large pulmonary cavity, as is well illustrated in Cases 6 and 7 here reported. Such anomalous findings at necropsy have been reported by many clinicians and roentgenographers. It seems to me that in such doubtful cases fluoroscopy is of more value than roentgenography. In localized pneumothorax we often see the mediastinum rhythmically moving during the respiratory act; during inspiration it is moved toward the affected side. This is best seen in artificial pneumothorax, after the first one or two fillings, when there is but a small air pouch in the pleura. In the spontaneous variety, when the adhesions are not dense enough to hold the mediastinum very fast, we may observe the same phenomenon, and this is never seen in cases of large cavities. In most cases it is, however, easy to differentiate on the roentgenogram between cavities and localized pneumothorax. In extensive disease, pulmonary cavities are usually

multiple; they contain not only air, but also secretions which are not constant in quantity, changing intermittently, and bridges made up of connective tissue and blood vessels. No clear, bright area lacking in lung markings is, as a rule, produced on the roentgenogram; their margins are more opaque and the pulmonary tissue around them is denser than in localized pneumothorax. Bearing these points in mind, we may differentiate the two conditions in most doubtful cases. In some, as we have shown, this is impossible.

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STUDIES ON BLOOD SUGAR*

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I

ALIMENTARY HYPERGLYCEMIA AND GLYCOSURIA AS A TEST OF SUGAR TOLERANCE

Jacobsen,[1] in 1913, published an interesting study of the effects of different food stuffs on the blood sugar. The food was given from two to three hours after a light breakfast and the blood sugar estimated by Bang's micromethod at short intervals thereafter. He found that protein and fat have no influence on the blood sugar, but that carbohydrate produces a rapid and often a marked hyperglycemia. Following the administration of 100 gm. of glucose, the blood sugar, according to Jacobsen, rises rapidly, often going to 0.16 per cent. and higher, and then falls more gradually to the original level or in some instances even to a lower level, the whole reaction lasting from one to three hours.

A perusal of Jacobsen's results suggested the use of a similar method to study carbohydrate tolerance. Perhaps the character of the curve might be altered in different diseases, and the test therefore yield important clinical data. In spite of the complex mechanism of carbohydrate metabolism, and our scant knowledge of the part played by the different factors concerned in the storage, mobilization and utilization of sugar, the simple estimation of a patient's ability to dispose promptly of a certain amount of glucose taken at one time into the stomach, or as usually named, his glucose tolerance, has definite clinical value. The method generally employed for this purpose is to feed patients glucose in increasing amounts until sugar appears in the urine. There are difficulties and inconveniences in the way of carrying on such an investigation. It is rarely possible to hit on the proper amount of glucose at the first dose, and therefore the test must be repeated a number of times. Solutions of glucose above 100 gm. make a nauseous draught for most patients. Not infrequently they vomit the mixture, and the test must be abandoned. Besides these difficulties, there are also sources of error in the method because

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* From the Medical Clinic of the Johns Hopkins Hospital.
1. Jacobsen: Biochem. Ztschr., 1913, **56**, 471.

no account is taken of the renal threshold for glucose. Sometimes otherwise normal persons have a low renal threshold and sugar appears in the urine although the blood sugar is only a little raised; more commonly still, renal permeability is decreased and little sugar or none comes out in the urine although the blood sugar mounts to a high level. Under such circumstances one would conclude erroneously, in the first instance, that the patient had a low sugar tolerance; in the second instance, a high sugar tolerance. It would be a decided advantage could we give a single and constant dose of glucose and from a study of the patient's reaction satisfactorily determine the sugar tolerance. We believe that the method we have employed furnishes us this information in an altogether satisfactory way, and that it adds, besides, an insight into the carbohydrate economy that the rougher tolerance test does not give.

METHOD

The patient to be tested receives 100 gm. of glucose in a lemonade in the morning after the night fast. We have found it advisable to prepare the lemonade by dissolving the glucose in warm water, adding the juice of several lemons, or of two lemons and an orange, making the mixture up to 300 c.c., and cooling by packing in ice, or by adding ice before serving. Such a mixture is not disagreeable to take, and rarely causes nausea. If larger quantities of water are used patients often complain of the bulk, and sometimes of nausea after drinking it. The blood sugar is determined before the glucose is given, and thereafter at frequent intervals. Specimens of urine are collected immediately before or immediately after each blood specimen is taken; or, if the patient is unable to void so frequently, as often as they can be obtained. The urine is carefully examined for sugar, and if sufficient be present the quantity is determined separately in each specimen. The blood is obtained by puncture of an arm vein at the bend of the elbow, a little over 2 c.c. of blood being withdrawn at each puncture. It may seem a formidable procedure to undertake so many venipunctures at short intervals, but in fact it is neither difficult for the operator nor disagreeable to the patient. If a vein has once been fairly entered the needle may thereafter be passed in through the same puncture and the patient scarcely be aware of the operation. The only important warning is to avoid making suction until the needle is fairly in the vein, and to desist before the needle is withdrawn. A small hematoma may so obscure the location of the vein that another site must be selected for the next puncture. In fat subjects this is often a disadvantage. We are assured by patients who have had experience with both methods that repeated pricking of the ear or finger tip is more dis-

agreeble than an equal number of venipunctures skilfully performed. In these studies we have made more frequent blood sugar determinations than are really necessary. We believe that four determinations, one before administering the glucose, and others a half hour, one hour and two hours after, will give all needed information.

We have used the Lewis-Benedict[2] blood sugar method following the technic originally described. Numerous control estimations on glucose solutions of known strength have convinced us of the remarkable accuracy of the method. Heating the mixture in a test tube over a free flame is tedious and time consuming, but we have been unable to get accurate results in other ways, and we have tried heating over a steam bath and in the autoclave at different pressures. In examining the urine Benedict's[3] qualitative and quantitative methods were employed.

REACTIONS IN NORMAL PERSONS

Jacobsen's studies on alimentary hyperglycemia following the administration of 100 gm. of glucose were made on fourteen so-called normal persons. The blood sugar rose to a maximal concentration of from 0.12 per cent. to 0.23 per cent. The rise occurred rapidly, the highest point being reached in from fifteen minutes to one hour, the fall more gradually, the reaction occupying from forty-five minutes to three and one-half hours. Most of the persons tested by Jacobsen had a single urine examination, but some had two, and a few three. The six whose blood sugar did not rise above 0.16 per cent. had no sugar in the urine; the eight whose blood sugar went above 0.17 per cent. did have glycosuria.

We are unwilling to allow that Jacobsen's figures be accepted as the standard for normals. It is generally conceded that normal persons do not have sugar in the urine after the ingestion of 100 gm. of glucose, even when the glucose is taken into a fasting stomach. Undoubtedly most of Jacobsen's subjects had a somewhat lowered carbohydrate tolerance. Our results, as well as those obtained by Hopkins, support this contention.

Hopkins[4] has studied the effects of 100 gm. of glucose on eight normal persons. The blood sugar rose to a maximal concentration of from 0.11 per cent. to 0.156 per cent., the highest point being reached in from thirty minutes to two hours. In the six instances followed to the end of the reaction, the reaction occupied from one and a half to three and a half hours. No urine examinations are reported.

2. Lewis and Benedict: Jour. Biol. Chem., 1915, **20,** 61.
3. Benedict: Jour. Am. Med. Assn., 1911, **57,** 1193.
4. Hopkins: Am. Jour. Med. Sc., 1915, **102,** 254.

In Chart 1* is given the results of our study of six normal persons. After 100 gm. of glucose the blood sugar rose to a maximal concentration of from 0.1 per cent. to 0.13 per cent. The rise to 0.148 per cent. was after 200 gm. of glucose. The high point was reached in from twenty minutes to one and a half hours. The whole reaction occupied from one to two hours. Although the blood sugar of none of the six rose to 0.15 per cent. still two showed glycosuria. In one of these the blood sugar went to 0.124 per cent., in the other to 0.138 per cent. (Charts 2 and 17). We have established, as will subsequently appear, that the normal renal threshold for glucose is between 0.17 per cent. and 0.18 per cent. of blood concentration. Therefore, these two patients have an unusually low renal threshold; perhaps one might speak of it as a potential renal diabetes.

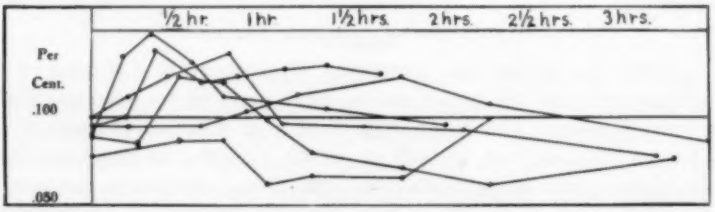

Chart 1.—A composite chart illustrating the blood sugar curve in five healthy persons after the ingestion of 100 gm. of glucose, and in one after 200 gm.

SUMMARY

In normal persons, after the ingestion of 100 gm. of glucose the blood sugar rises promptly to a level not exceeding 0.15 per cent.; the high point is reached usually in about thirty minutes; from the high point the blood sugar may fall off as quickly as it arose, but as a rule the fall is more gradual; the whole reaction lasts from one to two hours, occasionally longer. A certain number of otherwise normal persons have a low renal threshold for glucose so that sugar appears in the urine, although the blood sugar remains below 0.14 per cent.

*In the charts the heavy line represents the blood sugar curve, each dot on the curve denoting a blood sugar estimation. The base line is drawn at 0.1 per cent. since the blood sugar level of fasting normal persons never exceeds this amount. In the adrenalin charts the systolic and diastolic blood pressure readings are marked by fainter solid lines. The scale to the left of the chart serves for both the blood sugar and the blood pressure, that is, 0.150, for instance, indicates 0.150 per cent. of blood sugar, and 150 mm. Hg of pressure. At the bottom of the chart the diuresis and the glycosuria are portrayed; the diuresis by the solid line and the glycosuria by the shaded area. Each dot on the line shows the time at which a specimen of urine was collected. Since the intervals between specimens are irregular the diuresis and the glycosuria are expressed not as absolute figures, but as the rate of flow per hour. The scale to the right of the chart records the diuresis in cubic centimeters, the glycosuria in grams.

CASE 1.—I. H., W. M. S., healthy physician, aged 27, was given the glucose tolerance test, Nov. 29, and the epinephrin test, Nov. 17, 1915. The protocol of the first test is given in Table 1; the data of the second are presented in Chart 17.

TABLE 1.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 1*

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:25	0.096		
8:40	Glucose, 150 gm. in 450 c.c. water		
8:51	0.10	90	0
9:01	0.138	60	0
917	0.120	94	Trace
9:30	0.128	230	Trace
9:46	0.128	770	Trace
10:00	0.130	923	0
10:18	0.126	868	

* From 8 a. m. to 9:30 a. m. the patient drank 1,300 c.c. water.

CASE 2.—H. C., W. M. S., healthy medical student, aged 23, was given the epinephrin test Nov. 17, the glucose tolerance test, Dec. 6, and the atropin-epinephrin test, Dec. 29, 1915. The protocols of the first two tests are given in Tables 2 and 3, respectively; the data of the last test are presented in Chart 18.

TABLE 2.—PROTOCOL OF EPINEPHRIN TEST IN CASE 2*

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:00	Glucose, 50 gm. in 400 c.c. water		
8:45	0.072		
8:50	Epinephrin, 1 mg.		
9:05	0.096		
9:20	0.138	?	0
9:30	0.166	450	1.8
9:40	0.174	444	2.4
10:00	0.154	600	3.0
10:15	0.132	624	2.5
10:30	0.12		
10:40	0.092	320	0.4
11:00	0.068		
11:30	.....	245	

* From 8:50 to 11 the patient drank 1,700 c.c. water.

TABLE 3.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 2

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. per Hour
8:38	0.091		
8:40	Glucose, 200 gm. in 500 c.c. water		
8:50	0.135		
9:00	0.148		
9:10	0.132		
9:25	0.112	143	0
10:00	0.105		
10:40	0.096	175	0

CASE 3.—M. McN., W. M. S., healthy medical student, aged 24, was given the glucose tolerance test, Jan. 14, and the epinephrin test, Feb. 21, 1916. The protocols of these tests are given in Tables 4 and 5, respectively.

TABLE 4.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 3

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:25	0.096		
8:30	Glucose, 100 gm. in 300 c.c. water		
8:42	0.095	44	0
9:07	0.095	374	0
9:23	0.104	572	0
9:40	0.114	60	0
10:15	0.124	157	0
10:45	0.108	364	0
12:00	0.086	251	0

TABLE 5.—Protocol of Epinephrin Test in Case 3

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:48	0.088		
8:50	Glucose, 50 gm. in 200 c.c. water		
9:00	Epinephrin, 1 mg.		
9:00	0.115	70	0
9:10	0.126		
9:25	0.172		
9:35	0.255	155	0.39
9:53	.....	824	5.06
10:10	0.284	645	7.9
10:45	0.182	116	1.7
11:37	0.085	80	0.98

Case 4.—H. G., W. M. S., healthy medical student, aged 24, was given the glucose tolerance test, Jan. 30, 1916. The protocol of this test is given in Table 6.

TABLE 6.—Protocol of Glucose Tolerance Test in Case 4

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:47	0.101		
9:00	Glucose, 100 gm. in 300 c.c. water		
9:10	0.112		
9:24	0.124		
9:45	0.137		
10:03	0.096		
10:30	0.095	91	0
11:04	0.094		
12:10	0.078	98	0

Case 5.—J. H., W. M. S., healthy medical student, aged 24, was given the glucose tolerance test, Feb. 3, 1916. The data of this test are presented in Chart 2.

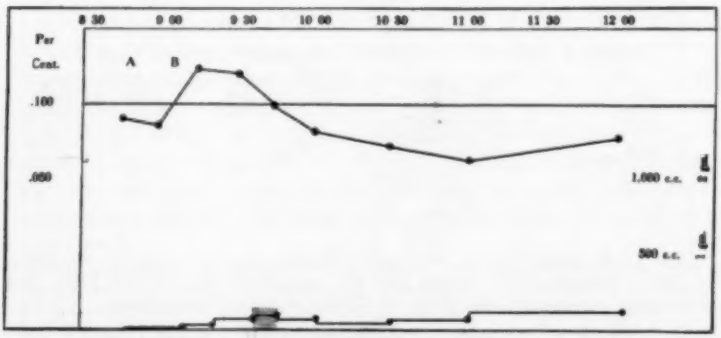

Chart 2 (Case 5).—Normal person. A normal reaction, except that the patient shows a remarkably low renal threshold. The rise is quick, the high point being reached thirty minutes after the ingestion of 100 gm. of glucose. There is no plateau, and the fall is rapid, the whole reaction being over in one hour. Although the blood sugar rises only to 0.124 per cent., a small amount of sugar appears in the urine. The renal threshold, therefore, is in the neighborhood of 0.12 per cent. There is no special diuresis. At 7 a. m. the patient voided. *A*, glucose, 100 gm. in 300 c.c. of water; *B*, water, 150 c.c.

CASE 6.—L. G., W. M. S., healthy medical student, aged 23, was given the glucose tolerance test, Feb. 10, 1916. The protocol of this test is given in Table 7.

TABLE 7.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 6

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:30	0.079		
8:45	Glucose, 100 gm. in 300 c.c. water		
9:00	0.084	98	0
9:15	0.086	93	0
9:30	0.087	100	0
9:46	0.061	405	0
10:00	0.067	385	0
10:30	0.066	464	0
11:00	0.100	104	0

REACTIONS IN DIABETES

Jacobsen reports the effects of 50 gm. of white bread on the blood sugar of five diabetics. Three of the cases were sugar-free when the test was begun; the other two had respectively 0.6 per cent. and 0.36 per cent. of sugar in the urine. Following the administration of 50 gm. of bread, the equivalent of 27 gm. of glucose, the blood sugar rose rapidly, but somewhat slower than in normals, the high point being reached in from one to one and a half hours; this high point was maintained for from thirty minutes to an hour, giving the curve a rounded, instead of a sharp summit; the fall was then gradual, the whole reaction occupying from two to over three hours. In two of the patients, sugar free at the start, the blood sugar did not reach 0.15 per cent., and still appreciable amounts of sugar appeared in the urine. Jacobsen comments on this disproportion, stating that diabetics excrete more sugar at a given blood sugar level than do normals. We have found that in diabetes the renal threshold is often abnormally low and this low threshold is the cause of the difference Jacobsen has noted.

Hopkins has studied the hyperglycemia following the administration of 100 gm. of glucose in nine diabetics. All of these patients had a high blood sugar and glycosuria when the test was given. Hopkins comments on the pronounced hyperglycemia that followed, and the prolongation of the reaction as compared with normals.

We have studied twelve reactions on nine diabetics, administering from 10 to 100 gm. of glucose, according to the severity of the disease. The severity of the disease was judged by the ease with which the patients were rendered sugar free by fasting and their ability subsequently to utilize carbohydrate without the appearance of glycosuria. The cases are thus roughly divided into mild, moderately severe and severe diabetes. Three of the four patients classed as mild diabetics, received 100 gm. of glucose, the other 85 gm. The general clinical

features of the four cases, 7, 8, 9, and 10, and the results of the test are as follows:

CASE 7 (Dispensary No. F-51051).—Diagnosis: diabetes mellitus. B. C., W. M. M., aged 40, gave a history of onset of illness occurring in November, 1915, with polyuria and polydipsia. The patient lost 12 pounds in weight. Examination on Feb. 8, 1916, was quite negative, except for glycosuria. The patient became sugar-free on carbohydrate restriction. The glucose tolerance test was made March 3, 1916. The data of this test are presented in Chart 3.

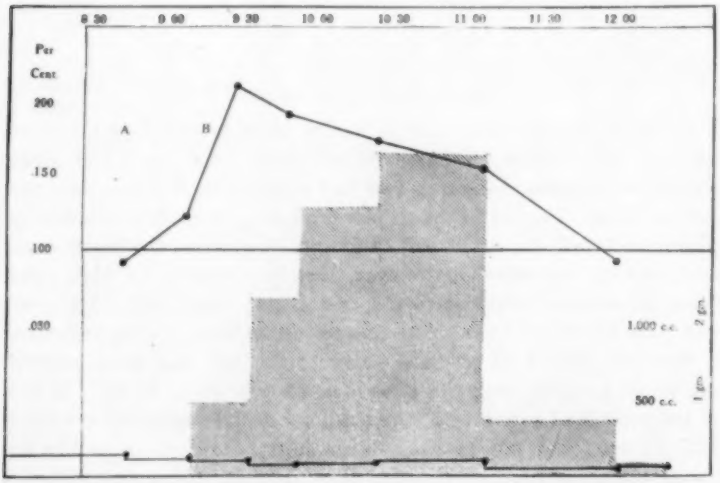

Chart 3 (Case 7).—A characteristic chart from a mild diabetic. The blood sugar rise is rapid, and quite high, the high point being reached three quarters of an hour after taking the glucose. There is no well marked plateau, but the fall is slow and gradual, the whole reaction lasting three and one-quarter hours. On the rise the renal threshold is somewhere between 0.124 per cent. and 0.21 per cent. Since a large amount of sugar is put out in this period, the renal threshold probably is in the neighborhood of 0.18 per cent. This chart shows how the threshold falls as sugar is excreted, for on the down-curve some sugar is still put out even after the blood sugar has fallen as low as 0.094 per cent. There is no special diuresis. During the period of the experiment 6.8 gm. of sugar are excreted. At 8 a. m. the patient voided. *A*, glucose, 100 gm. in 300 c.c. of water; *B*, water, 150 c.c.

CASE 8 (Hospital No. 35464).—Diagnosis: diabetes mellitus; angina pectoris; slight hypertension. D. R., W. F. W., aged 53, had had mild attacks of angina for eight years. Sugar was discovered in the urine by a physician, but no symptoms of diabetes were found. On admission to the hospital, Nov. 12, 1915, examination showed an obese woman, signs of slight pulmonary emphysema, blood pressure 160 and 110, abundant sugar in the urine, and slight acetonuria. The patient quickly became sugar-free, and no sugar returned, on carbohydrate-free diet of 1,500 calories with 90 gm. of white bread. Blood sugar on admission was 0.206 per cent.; on March 1, 1916, 0.128 per cent. The glucose tolerance test was made March 6, 1916. The protocol of this test is given in Table 8.

TABLE 8.—Protocol of the Glucose Tolerance Test in Case 8

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:45	0.091	142	0
8:48	Glucose, 100 gm. in 300 c.c. water		
9:10	0.124	122	0
9:30	0.210	110	1
9:50	0.190	83	2.4
10:25	0.174	94	3.6
11:07	0.155	102	4.3
12:00	0.094	52	0.8
12:21	.....	66	0.13

Case 9.—F. R., W. M. M., aged 46, came for treatment on April 12, 1915, for an acne rosacea of long standing, and a primary syphilitic sore. Routine examination disclosed a postprandial glycosuria, the morning urine never containing sugar. The glucose tolerance test was made March 13, 1916. The data of this test are presented in Chart 4.

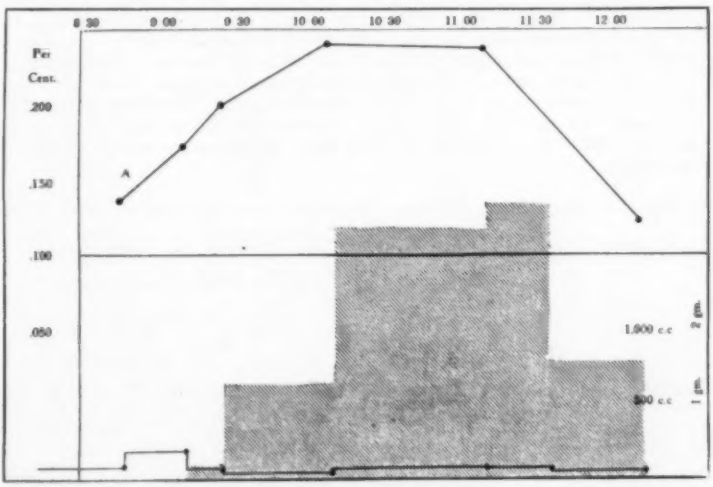

Chart 4 (Case 9).—A characteristic diabetic blood-sugar chart. The rise is a little slow (one and one-half hours); the plateau sustained (one hour); the drop rather abrupt. The threshold on the rise is between 0.171 per cent. and 0.2 per cent. Since a moderate amount of sugar is put out and the rise is abrupt, the renal threshold is in the neighborhood of 0.18 per cent. The threshold on the down-curve is lower than on the up-curve, although it cannot be definitely fixed in the chart. The diuresis is fairly constant, and bears no relation to the glycosuria. During the period of the experiment 7 gm. of sugar are excreted. At 6 a. m. the patient voided, and at 7 a. m., drank a glass of sweetened lemonade. *A*, glucose, 100 gm. in 300 c.c. of water.

Case 10 (Hospital No. 35907).—Diagnosis: diabetes mellitus, mild. Discovery was made in the summer of 1915 that the urine of F. V., M. W. M., aged 52, reduced Fehling's solution. The reducing body was decided to be glycuronic acid. The patient came to the hospital in May, 1916, for burning on urination, and sugar was discovered in the urine. No symptoms of diabetes were found. The glucose tolerance test was made, May 26, 1916. The protocol of this test is given in Table 9.

TABLE 9.—Protocol of the Glucose Tolerance Test in Case 10

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:50	0.103	42	0
9:00	Glucose, 100 gm. in 300 c.c. water		
9:30	0.167	60	0
10:07	0.195	305	6.76
10:45	0.205	426	1.92
11:32	0.182	330	1.65
12:30	0.09	168	Trace

Of the three moderately severe cases, in two, Cases 11 and 12, the test was repeated. The general clinical features of each case, and the results of the test, are as follows:

Case 11 (Hospital No. 34967).—Diagnosis: diabetes mellitus. C. H. O., M. W. W., aged 25, gave a history of onset of symptoms occurring in October, 1915, with polydipsia, polyuria and loss of weight. On admission to the hospital, Nov. 15, 1915, there was abundant glycosuria and moderate acetonuria. The physical examination showed nothing of importance except the loss of weight. The patient rapidly became sugar-free on fasting. Subsequently a diet containing 80 gm. of carbohydrate caused hyperglycemia (0.136 per cent.) but no glycosuria. The blood sugar on admission was 0.38 per cent.; three days later, 0.08 per cent. The glucose tolerance test was made Nov. 8 and Nov. 12, 1915. The protocols of these tests are given in Tables 10 and 11, respectively.

TABLE 10.—Protocol of Glucose Tolerance Test in Case 11, Nov. 8, 1915

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
9:15	0.072		
9:20	Glucose, 10 gm.		
9:35	0.070		
9:55	0.085		
10:10	0.095		
10:30	.....	?	0
10:50	0.096		
11:15	0.085	?	0

TABLE 11.—Protocol of Glucose Tolerance Test in Case 11, Nov. 12, 1915

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
6:30	Carbohydrate-free breakfast		
9:00	0.06		
9:15	Glucose, 50 gm.		
9:45	0.09		
10:00	0.132		0
10:15	0.142	?	
10:30	0.161	93	2.23
10:45	0.184		
11:00	.....	88	2.30
11:30	.....	147	1.13

Case 12 (Hospital No. 38325).—Diagnosis: diabetes mellitus; arteriosclerosis; hypertension; chronic nephritis (vascular); chronic infectious arthritis; oral sepsis; Dupuytren's contracture; facial parlysis (old). The patient applied to the surgical department for relief from the Dupuytren's contractures. Glycosuria was discovered during the routine examination. On admission to the medical department, Nov. 4, 1915, D. V., W. M. M., aged 60, had moderate glycosuria without acetonuria. The patient was almost sugar-free on slightly restricted diet, and completely sugar-free after a twenty-four-hour fast. There was no glycosuria on a diet containing 75 gm. of carbohydrate. The blood sugar on admission was 0.17 per cent.; on discharge, 0.09 per cent. The blood pressure was 155 and 100. The phenolsulphonephthalein test, made Nov. 13, 1915, was 47 per cent.; Nov. 24, 1915, 47 per cent. The glucose tolerance test

was made Nov. 10, the epinephrin test, Nov. 22, 1915. The data of these tests are presented in Charts 5 and 20, respectively.

CASE 13 (Hospital No. 35469).—Diagnosis: diabetes mellitus. J. J. B., W. M. S., aged 33, gave a history of onset of symptoms occurring October, 1915. Polydipsia and polyuria developed. In January, 1916, digestive disturbances occurred with 25 pounds loss of weight. On admission to the hospital, Feb. 16, 1916, the examination was essentially negative, except for abundant glycosuria and moderate acetonuria. The patient was sugar-free after three days' starvation. On discharge, March 10, 1916, a trace of sugar was found in the urine after 40 gm. of glucose; no sugar was found on a 2,000 calory diet consisting of 140 gm. protein, 40 gm. carbohydrate and 140 gm. fat. The blood sugar on admission was 0.31 per cent.; on discharge, 0.07 per cent. The carbohydrate tolerance test was made February 25 and March 10, 1916, respectively. The protocol of the first test is given in Table 12; the data for the second test are presented in Chart 6.

TABLE 12.—PROTOCOL OF CARBOHYDRATE TOLERANCE TEST IN CASE 13, FEB. 25, 1916

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:35	0.134	48	0
8:38	Glucose, 40 gm. in 300 c.c. water		
9:00	0.171	139	0
9:30	0.210	97	0.3
9:40	0.288	168	1.68
10:00	0.262	265	2.70
10:48	0.260	277	1.80
11:44	0.264	295	0.97
11:57	.....	120	0.31

The general clinical features of the two severe cases, 14 and 15, and the results of the test are as follows:

CASE 14 (Hospital No. 35506).—Diagnosis: diabetes mellitus; furunculosis; oral sepsis. P. D., W. M. M., aged 39, gave a history of onset of symptoms occurring December, 1915, polydipsia, polyuria and loss of weight. The symptoms were severe for two months, with 60 pounds' loss of weight. The physical examination was negative, except for oral sepsis and furuncle on left forearm. On admission to the hospital, March, 1916, there was abundant sugar, acetone and aceto-acetic acid in the urine. After three days' starvation glycosuria and acetonuria were still present. On discharge, March 18, 1916, the patient was sugar-free on a 1,500 calory diet consisting of 80 gm. protein, 125 gm. fat and 17 gm. carbohydrate. The blood sugar on admission was 0.36 per cent.; on discharge, 0.117 per cent. The carbohydrate tolerance test was made March 17, 1916. The data of this test are presented in Chart 7.

CASE 15 (Hospital No. 35719).—Diagnosis: diabetes mellitus. C. S., W. M. M., aged 24, gave a history of onset of symptoms occurring one year before admission to hospital with weakness, polydipsia and polyuria. The patient was under dietetic treatment most of the year without much improvement. Examination on admission, Feb. 26, 1916, showed a sallow, poorly nourished man, without other important findings. The urine contained abundant sugar, aceto-acetic acid and acetone. The blood sugar was 0.241 per cent.; the alveolar carbon dioxid, 22. After three days' starvation the urine became sugar-free but the acetonuria increased. On a diet of 1,600 calories containing 20 gm. carbohydrate, a small amount of sugar appeared in the urine. The patient finally became sugar free on diet of 1,600 calories containing 9 gm. carbohydrate. On discharge, April 25, 1916, the patient was sugar-free on a diet of 1,500 calories containing 30 to 45 gm. carbohydrate. The blood sugar, March 17, 1916, was 0.146 per cent.; April 4, 1916, 0.119 per cent. The glucose tolerance test was made April 10, 1916. The data of this test are presented in Chart 8.

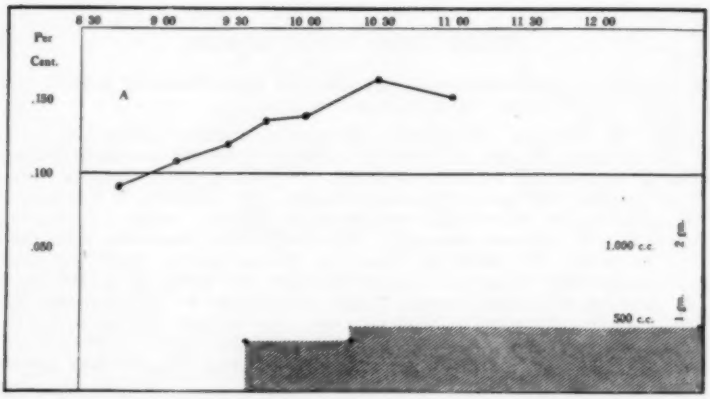

Chart 5 (Case 12).—A typical diabetic chart. The rise is slow, the high point being reached one and three quarters hours after the administration of 50 gm. of glucose. The plateau is sustained, and there is only a little falling off from the high point after two and one-quarter hours. Sugar was excreted before the blood sugar reached 0.15 per cent. The exact threshold cannot be determined. There is no striking diuresis. During the experiment 1.6 gm. of sugar are excreted. At 6:30 a. m. the patient was given a carbohydrate free breakfast. *A*, glucose, 50 gm.

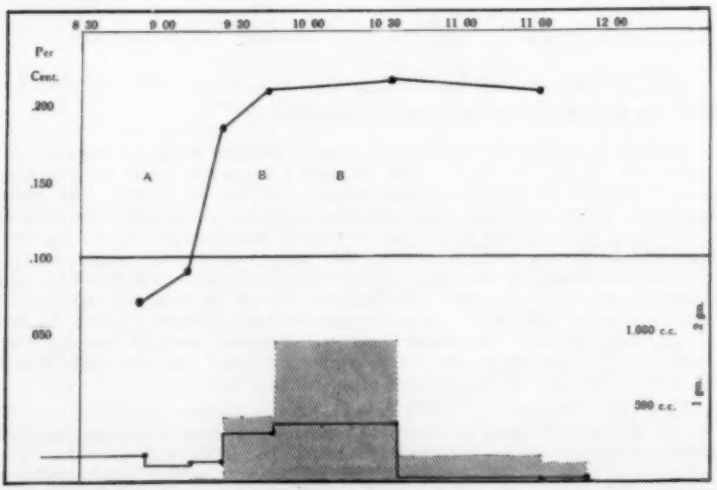

Chart 6 (Case 13).—A characteristic diabetic chart, without lowering of the renal threshold. The rise is very abrupt, the high point being reached forty-five minutes after the administration of the glucose. There is a well sustained plateau, the curve just beginning to fall after two and one-half hours. Judging from the large amount of sugar put out in the specimen passed at 10:35 it is probable that in the preceding period the blood sugar rose higher than is indicated on the chart. Since only a trace of sugar is passed in the urine collected at 9:26 when the blood sugar was 0.185 per cent. the renal threshold is evidently somewhere in the neighborhood of 0.18 per cent. There is a moderate diuresis during the period of marked glycosuria. During the experiment 2.3 gm. of sugar are excreted. At 8:15 a. m. the patient voided. *A*, glucose, 40 gm. in 300 c.c. of water; *B*, water, 100 c.c.

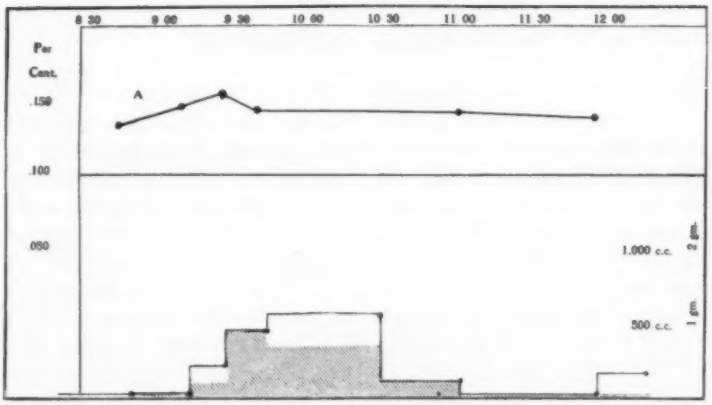

Chart 7 (Case 14).—A characteristic diabetic blood sugar curve, after the administration of 20 gm. of glucose. The blood sugar, high to begin with, rises only a little, the high point being reached in thirty-five minutes. There is then a slight drop; but a point higher than the original level is maintained for over three hours. The threshold is below 0.146 per cent., very likely in the neighborhood of 0.14 per cent. On the down-curve sugar is still excreted after the blood sugar has reached 0.139 per cent. The diuresis during the period of glycosuria is striking, and altogether out of proportion to the amount of sugar excreted. The period of greatest sugar excretion comes immediately after the high point on the blood sugar curve. The total amount of sugar excreted during the experiment is 1.1 gm. At 6:30 a. m. the patient voided. *A*, glucose, 20 gm. in 300 c.c. of water .

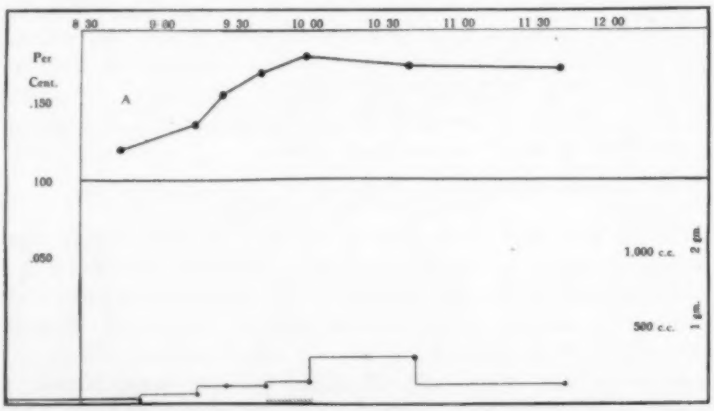

Chart 8 (Case 15).—A characteristic diabetic reaction after 15 gm. of glucose. The blood sugar rises rather slowly, the high point being reached one hour after the ingestion of glucose. Although the reaction extends over three hours, there is at the end of this period just a beginning tendency for the blood sugar to fall off. Only one specimen of urine shows sugar, and this shows only a trace. The threshold, therefore, is accurately fixed in the neighborhood of 0.18 per cent. since the specimen collected when the blood sugar had fallen to 0.178 per cent. no longer contains sugar. There is a rising diuresis, with the rising blood sugar. The kidneys react readily with diuresis, even though there is no glycosuria. At 8 a. m. the patient voided; *A*, glucose, 15 gm. in 300 c.c. of water.

SUMMARY

The reaction of diabetics to the ingestion of glucose was very different from the reaction of normal persons. Our studies do not give strictly comparable data, for only three of the diabetics received 100 gm. of glucose. These three patients, however, having but a mild derangement of carbohydrate metabolism, illustrate strikingly the change in the diabetic reaction as contrasted with the normal. All three had moderate glycosuria during the test, excreting respectively, 6.8 gm., 7 gm. and 3 gm. of sugar. Case 10 had a well marked diuresis during the period of glycosuria, but the large amount of water taken by the patient may account for this. The blood sugar rose more slowly than in the normal, the highest point being reached after forty-five minutes, after one hour and twenty minutes and after one hour and forty-five minutes. It also rose to a much higher level, all three exceeding 0.2 per cent. This high point was maintained for nearly an hour in two instances, for only a short period in the other. The fall of the blood sugar occurred much more slowly than in the normal, the whole reaction occupying from three to four hours.

These general features of the diabetic blood sugar curve are faithfully reproduced by the other patients receiving, on account of the severity of their disease, smaller amounts of glucose. In some of the curves the blood sugar was just beginning to drop three hours after taking the glucose. Apparently the duration of the reaction is a more important index of the severity of the alteration of carbohydrate metabolism than the height of the reaction. In some of the patients a definite diuresis accompanied the glycosuria, and the tendency was particularly noticeable in the severe cases.

REACTIONS IN NEPHRITIS

It has long been known that in nephritis the blood sugar is often unusually high.[5] However, it is not always high, sometimes it is at the normal level; and why some cases have hyperglycemia and others have not has never been satisfactorily explained. Attempts to bring the hyperglycemia into relation with the blood pressure have not been wholly successful. Hopkins reports a large number of single blood sugar observations on patients with nephritis, and in addition gives the results of an alimentary test on four of the cases. Three of these show a marked hyperglycemia after 100 gm. of glucose, two going above 0.2 per cent. The high point is fairly well sustained,

5. Bang: Der Blutzucker, Weisbaden, 1913, p. 128. Rolly and Oppermann: Biochem. Ztschr., 1913, **48,** 268. Bing and Jacobsen: Deutsch. Arch. f. klin. Med., 1914, **114,** 57. Hopkins: Footnote 4. Myers and Bailey: Jour. Biol. Chem., 1916, **24,** 147.

at least the summit of the curve is rounded, and the fall is rather slow, the reaction occupying from three to four hours.

We have made observations on six patients with nephritis. A brief summary of the clinical features of the cases, 16, 17, 18, 19, 20 and 21, and the results of the test follows:

CASE 16 (Hospital No. 35779).—Diagnosis: chronic nephritis; hypertension; arteriosclerosis; myocardial insufficiency; uremia. H. H., B. M. M., aged 49, admitted complaining of shortness of breath. There was an onset of symptoms five months before, with polyuria and nocturia. There was some dyspnea for a year and headaches. On admission to the hospital, March 22, 1916, examination showed a poorly nourished man; Cheyne-Stokes breathing; albuminuric retinitis; cardiac enlargement with systolic murmur and presystolic gallop; thickened vessels; blood pressure 258:180, and slight edema of the ankles. Abundant albumin and casts were found in the urine. The phenolsulphonephthalein test was 30 per cent. and on April 9, 1916, a trace. A progressively downward course terminating in death, May 4, 1916. The anatomic diagnosis revealed primary arteriosclerosis involving particularly the renal arteries, cardiac hypertrophy and dilatation and chronic passive congestion of the viscera. The glucose tolerance test was made March 24, 1916. The data of this test are presented in Chart 9.

CASE 17 (Hospital No. 35716).—Diagnosis: arteriosclerosis; hypertension; chronic nephritis; myocardial insufficiency; chronic bronchitis. L. H., B. F. W., aged 50, gave a history of onset of symptoms occurring over a year before, with dyspnea, cough and wheezing. The symptoms aggravated during the past few months. On admission to the hospital, March 30, 1916, examination showed bronchitis; heart enlarged with loud systolic murmur; diffuse thickening of peripheral vessels; blood pressure 225:130, and edema of legs and over sacrum. The phenolsulphonephthalein test was 37 per cent. Albumin and casts were found in the urine. A renal test meal was given. There was marked nocturnal polyuria with low specific gravity and poor excretion of nitrogen. The glucose tolerance test was given April 3, 1916, the protocol of which is given in Table 13.

TABLE 13.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 17

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
9:05	0.105		
9:15	Glucose, 100 gm. in 300 c.c. water		
9:30	0.118	19	0
10:00	0.158	54	0
10:35	0.174	91	0
11:10	0.160		
12:00	0.128	45	0

CASE 18 (Dispensary No. F-10382).—Diagnosis: chronic nephritis; hypertension; dilated aortic arch. M. G., W. M. M., aged 45, gave a history of cough, expectoration and dyspnea for three years. Examination, April 22, 1916, showed an obese man with extreme pyorrhea alveolaris; scattered pulmonary râles; enlarged heart with ringing aortic second sound, manubrial dulness; diffuse arteriosclerosis and blood pressure 240:148. Albumin and casts were found in the urine. The phenolsulphonephthalein test was 33 per cent. The glucose tolerance test was made April 24, 1916. The data of this test are presented in Chart 10.

CASE 19 (Hospital No. 35659).—Diagnosis: chronic diffuse nephritis (?); hypertension and chronic appendicitis. J. S., W. M. M., aged 28, had had

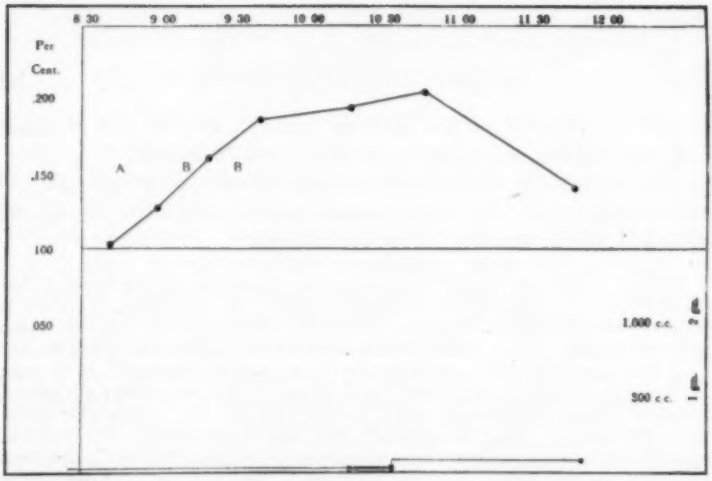

Chart 9 (Case 16).—A diabetic type of chart, with high renal threshold, in a nephritic. The rise is very gradual, the highest point being reached two hours after the administration of glucose. There is a well marked plateau during the second hour. The fall is gradual, and the whole reaction is not over two and one-half hours after taking the glucose. Although the blood sugar goes to 0.205 per cent., only a trace of sugar is excreted in the urine. The threshold is therefore considerably raised. There is no special diuresis. At 8:20 a. m. the patient voided. *A*, glucose, 100 gm. in 300 c.c. of water; *B*, water, 150 c.c.

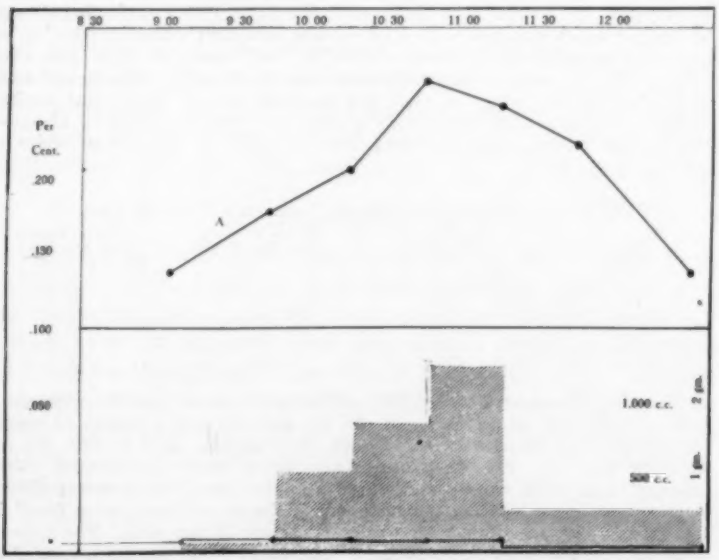

Chart 10 (Case 18).—A typical diabetic type of reaction with normal renal threshold in a patient with hypertension. The blood sugar, high at the outset, rose slowly, reaching the highest point in one hour and twenty minutes. The curve was flattened at the top and the fall was slow, the whole reaction lasting three hours. The renal threshold was in the neighborhood of 0.17 per cent. During the experiment 3.7 gm. of glucose were excreted. At 6:30 a. m. the patient voided; *A*, glucose, 100 gm. in 300 c.c. of water.

for a year and a half attacks of abdominal pain with hematuria. On admission to the hospital, April 13, 1916, examination showed slight general anasarca, blood pressure 188:126 and slight diffuse thickening of arterial walls. There was a trace of albumin in the urine but no casts. The phenolsulphonephthalein test was 78 per cent. A renal test meal was given. There was slight nocturnal polyuria and the specific gravity was fixed at a high level. The glucose tolerance test was made April 7, 1916. The protocol of this test is given in Table 14.

TABLE 14.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 19

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:20	0.106	21	0.08
8:30	Glucose, 100 gm. in 300 c.c. water		
9:10	0.149	54	0.14
9:30	0.161	63	0.13
10:00	0.164	34	0.08
10:30	0.137		
10:58	.....	43	0.12
11:00	0.120		
12:00	0.111	47	0.12

The results of the test were confused by presence of pentose in urine. Some glucose was excreted, as there was slight fermentation in the 9:31 specimen.

CASE 20 (Hospital No. 34529).—Diagnosis: chronic parenchymatous nephritis. J. S., W. M. S., aged 25, gave a history of onset of symptoms occurring shortly before admission, with edema. On admission to the hospital, Aug. 27, 1915, examination showed no noteworthy abnormalities except edema, abundant albumin and casts and a positive guaiac test in the urine. The phenolsulphonephthalein test was 68 per cent. Ambard's coefficient was 0.07. Blood urea nitrogen was 14 mg. per 100 c.c. A nephritic test meal was given; there was normal variation in specific gravity; polyuria and slight nocturnal polyuria were probably associated with elimination of edema. The blood pressure was 120:80. The glucose tolerance test was given April 13, 1916. The protocol of this test is given in Table 15.

TABLE 15.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 20

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:55	0.103	46	0
9:03	Glucose, 100 gm. in 300 c.c. water		
9:30	0.132	29	0
10:00	0.139	52	0
10:30	0.144	50	0
11:00	0.117	24	0
11:30	0.115	28	0
12:30	0.098	19	0

CASE 21 (Hospital No. 35945).—Diagnosis: chronic diffuse nephritis; hypertension; arteriosclerosis. J. B.. B. M. S., aged 25, gave a history of onset of symptoms occurring two months before admission with dyspnea on exertion and pain in the abdomen and over the precordium. On admission to the hospital examination showed chronic tonsillitis; cardiac hypertrophy with presystolic gallop, and hypertension, 230:180. The vessel walls were diffusely thickened. The urine showed a trace of albumin and many hyalin and finely granular casts. The Wassermann reaction was negative. The phenolsulphonephthalein test was 39 per cent. A nephritic test meal was given, there was nocturnal polyuria and marked fixation of specific gravity at a low level. The first glucose tolerance test was given May 19, the second, June 1, 1916. The protocols of these tests are given in Tables 16 and 17, respectively.

TABLE 16.—Protocol of Glucose Tolerance Test in Case 21, May 19, 1916

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
6:30	By mistake, breakfast: oatmeal, toast, eggs		
8:45	0.094		
8:48	Glucose, 100 gm. in 300 c.c. water		
8:57	.....	21	0
9:15	0.123	8	0
9:30	0.112	13	0
10:00	0.103	14	0
10:37	0.100	14	0

TABLE 17.—Protocol of Glucose Tolerance Test in Case 21, June 1, 1916

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:10	0.092	111	0
8:15	Glucose, 100 gm. in 300 c.c. water		
8:45	0.132	89	0
9:15	0.134	318	0
9:45	0.128	273	0
10:17	0.124	232	0

SUMMARY

The patient (Case 16, Chart 9), with chronic diffuse nephritis and hypertension, bordering on uremia, had a definite "diabetic type" of blood sugar curve, but only a trace of sugar appeared in the urine, although the blood sugar went to 0.2 per cent. The fasting blood sugar was at the upper limit of normal. The renal impermeability explains the absence of glycosuria, in spite of the marked hyperglycemia, but it does not explain the profound disturbance of carbohydrate metabolism portrayed in the blood sugar curve.

The patient (Case 18), with marked hypertension and only moderately impaired renal function, showed a reaction altogether similar to the reaction of a mild diabetic (Chart 10). The fasting blood sugar was high, 0.136 per cent.; the renal threshold was 0.17 per cent.; the blood sugar mounted to 0.264 per cent.; the summit of the curve was rounded; the reaction occupied three hours; a large amount of sugar was excreted. Obviously in this instance renal impermeability played no part in producing hyperglycemia.

Another patient (Case 17) with hypertension and only a moderate impairment of renal function showed a similar though not so marked reaction. The blood sugar curve rose slowly, was rounded at the summit and fell slowly, but the highest point was at 0.174 per cent. and no sugar appeared in the urine.

In contrast with these three reactions is the reaction of the patient (Case 20) with chronic diffuse nephritis without hypertension. The blood sugar curve was a little more prolonged than the normal type, but it did not show the striking diabetic features of the others.

Another patient (Case 19) with chronic diffuse nephritis, without hypertension and with almost normal renal function, showed a some-

what higher and more prolonged blood sugar curve. The urine examinations were equivocal since all of the specimens contained pentose.

These observations influenceed us strongly to regard hypertension as an important indicator of disturbed carbohydrate metabolism, and tempted us to seek the common explanation for both in altered epinephrin function. However, a recent observation, temporarily at least, upset this speculation. This observation was made on the patient (Case 21) with chronic diffuse nephritis and hypertension with only moderately impaired renal function. Our first test performed two hours after breakfast yielded a perfectly normal reaction. Hoping that the breakfast might have been accountable for this unexpected result, the test was repeated. Again, a practically normal curve was obtained. In the face of this evidence, we cannot correlate hypertension and alimentary hyperglycemia.

Therefore, in many cases of nephritis there is a profound change in carbohydrate metabolism, the blood sugar curve after the ingestion of glucose resembling the "diabetic curve." When there is marked interference with renal function very small amounts of sugar or none appear in the urine, although the blood sugar may go above 0.2 per cent.

REACTIONS IN DISTURBANCE OF THYROID AND HYPOPHYSIAL FUNCTIONS

Excepting disease of the pancreas, disturbance of thyroid function is the most common cause of altered carbohydrate tolerance. The clinical manifestations of thyroid disease are notoriously variable, and the grouping of the different symptoms occurs in a confusing way. Vagotonic and sympathicotonic symptoms are often hopelessly mixed, and in one patient evidence of overfunction and underfunction may occur side by side. Sugar tolerance shows the same perplexing combinations. However, in a general way in hyperthyroidism it is low, and in hypothyroidism abnormally high, although individual patients display wide latitude in their response. It has been known for a long time that hyperglycemia commonly occurs in exophthalmic goiter, and recently the subject has been studied again in a thorough way by Geyelin.[6]

Since Cushing[7] has demonstrated the important part played by the hypophysis in carbohydrate economy, disturbance of hypophysial function has come to rank second only to thyroid disease as a fertile source of altered sugar tolerance. In disorders of this gland, as in thyroid disease, hyperfunction is associated with decreased tolerance, hypo-

6. Geyelin: The Archives Int. Med., 1915, **16,** 975.
7. Weed, Cushing and Jacobson: Bull. Johns Hopkins Hosp., 1913, **24,** 40.

function with an increase; but similar individual differences occur. Up to the present time, observations of carbohydrate tolerance in thyroid and hypophysial disease consist of urine examinations and of single or at most occasional blood sugar estimations. While these observations have established important facts they give no insight into the underlying metabolic disturbance. Only Hopkins has studied the curve of alimentary hyperglycemia in two cases of hypophysial disease. In both instances there was an abnormally high and prolonged reaction.

We have made observations on six patients with thyroid disease and five with hypophysial disorders. A brief report of the main clinical features of each case and the results of the test follows:

Case 22 (Hospital No. 38841).—Diagnosis: exophthalmic goiter. E. S., B. M. S., aged 21, had been nervous for three months, and had been growing weak. In October, 1915, exophthalmos was noted. Palpitation and tachycardia developed, with loss of weight. On admission to the hospital, examination showed a moderately emaciated colored man; marked exophthalmos; positive von Graefe's, Stellwag's and Joffroy's signs; struma with systolic thrill and bruit; marked tremor; slight enlargement of heart, and mononucleosis. The blood pressure was 136:64. Loewe's test was positive. The atropin reaction was moderate; the pilocarpin and epinephrin reactions slight. On Dec. 20, 1915, ligation of the superior and inferior thyroid arteries was performed, and on Jan. 8, 1916, left lobectomy was performed. The glucose tolerance test was made Jan. 7, 1916. The protocol of this test is given in Table 18.

TABLE 18.—Protocol of Glucose Tolerance Test in Case 22

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:30	0.080		
8:33	Glucose, 40 gm. in 300 c.c. water		
8:46	.....	35	0
9:00	0.224		
9:20	0.166		
9:40	0.154	93	1.22
10:00	0.210		
10:30	0.150		
11:00	0.126	85	1.0
12:00	0.120	103	0.43
3:20	.....	90	0

Case 23 (Hospital No. 38469).—Diagnosis: exophthalmic goiter. F. McD., W. M. M., aged 52, noticed loss of weight in October, 1914, and grew increasingly nervous, with shaking of hands and legs, palpitation and indigestion. Left lobectomy was performed March 1, 1915. Marked improvement followed the operation; the patient gained 30 pounds in weight. In December, 1916, there was a return of nervousness, palpitation, loss of weight and enlargement of thyroid. On admission to the hospital, Jan. 7, 1916, examination showed a neurotic, nervous man; marked tremor; slight von Graefe's sign; definite Möbius' sign; skin moist and warm; fulness of right lobe of thyroid; tachycardia, (94 to 106); mononucleosis, and moderate epinephrin, negative atropin and rather marked pilocarpin reaction. Right lobectomy was performed Jan. 24, 1915, followed by marked general improvement. The first glucose tolerance test was made Jan. 10, 1916, the second, Feb. 16, 1916. The data of these tests are presented in Chart 11.

Case 24 (Hospital No. 35150).—Diagnosis: exophthalmic goiter. J. O'C., W. M. S., aged 17, gave a history of onset of symptoms occurring two months

before admission, with swelling of neck and increasing prominence of eyes. Subsquently there was palpitation and nervousness. On admission to the hospital, Dec. 20, 1915, examination showed large, elastic struma with bruit and thrill; marked exophthalmos; epiphora; von Graefe's, Dalrymple's and Joffroy's signs; tendency to flushing; slight tremor; slight cardiac enlargement, and tachycardia (88 to 108). The glucose tolerance test was made Dec. 22 and the epinephrin, Dec. 27, 1915. The data of these tests are found in Charts 12 and 21, respectively.

CASE 25 (Hospital No. 39176).—Diagnosis: exophthalmic goiter. L. R., W. F. S., aged 31, gave a history of onset of illness occurring, Feb. 13, 1915, with an attack of grip. During convalescence tremor and trembling came on. The following month there were tachycardia and swelling of the thyroid. Subsequently the patient was very nervous. One attack of stubborn diarrhea occurred. There was hyperhidrosis. Examination on admission to the hospital, Feb. 18, 1916, showed emaciation; marked exophthalmos; moderately enlarged thyroid with slight thrill and bruit; von Graefe's sign, positive; Möbius' sign, slight; Joffroy's sign, negative; marked tremor; tachycardia (75 to 130); blood pressure 128:72; marked reaction to pilocarpin and moderate reaction to atropin and epinephrin. On March 17, 1916, a right lobectomy was performed. The glucose tolerance test was made Feb. 21, 1916. The data of this test are presented in Chart 13.

CASE 26 (Hospital No. 39426).—Diagnosis: exophthalmic goiter. J. R., W. F. M., aged 51, gave a history of onset of symptoms occurring June, 1913, with emotional disturbance, crying, etc., and nervousness. Exophthalmos came on shortly after. Subsequently there was loss of weight, tremor, hot flushes and goiter. A partial thyroidectomy was performed in March, 1914, followed by improvement. During the last four months symptoms returned: headache, flushing, nausea and vomiting, enlargement of goiter, palpitation, nervousness and fright. On admission to the hospital, March 2, 1916, examination showed extreme exophthalmos; marked dermatographia; von Graefe's sign, marked; Joffroy's sign, positive; Möbius' sign, positive; diplopia; struma with systolic thrill and bruit; slight enlargement of heart; moderate diffuse arteriosclerosis; hypertension, 156:72; fine tremor; Loewe's test, positive; marked epinephrin reaction; moderate atropin reaction, and slight pilocarpin reaction. The urine showed a trace of albumin. A left lobectomy was performed April 1, 1916. The glucose tolerance test was made March 31, 1916. The protocol of this test is given in Table 19.

TABLE 19.—PROTOCOL OF GLUCOSE TOLERANCE TEST IN CASE 26

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:30	0.108		
8:40	Glucose, 100 gm. in 300 c.c. water		
9:00	0.167	356	0
9:30	0.256	280	0
10:00	0.228	202	0.2
10:32	.....	280	0.3
11:00	0.095	316	0
11:30	.....	30	0
11:45	0.067		
12:10	.....	16	0

CASE 27 (Hospital No. 39846).—Diagnosis: colloid goiter. E. R., W. M. S., aged 16, gave a history of swelling in the neck which began eight years before admission to the hospital. Two years previous mechanical effects began to be noticed; dyspnea; difficulty in bending head; difficulty in swallowing and hoarseness. Physical examination showed nothing of importance other than the huge goiter. Subnormal temperature, slow pulse, dry skin and high sugar tolerance (300 gm. without glycosuria) point to slight hypothyroidism. On May 20, 1916, a right lobectomy was performed. The glucose tolerance test was made April 6, 1916. The protocol of this test is given in Table 20.

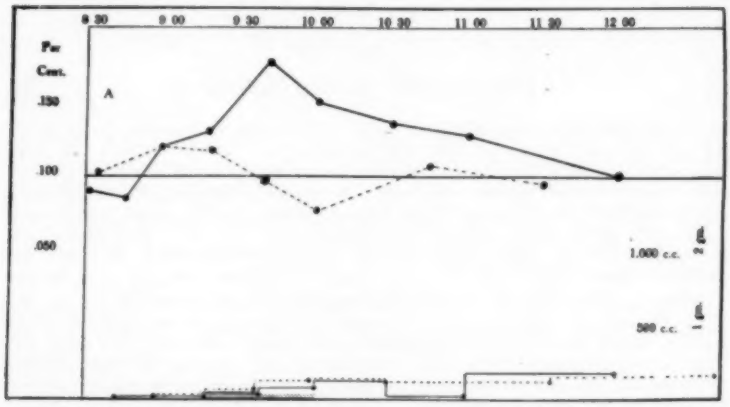

Chart 11 (Case 23).—The curve shows a rather marked and sustained blood sugar reaction after the administration of 100 gm. of glucose, in a patient with hyperthyroidism. The rise is slow, the high point being reached one hour and ten minutes after the administration of the glucose. There is no plateau, but there is a very gradual fall, the original level of blood sugar being reached after three and one-half hours. Sugar is excreted between 0.15 per cent. and 0.176 per cent. Since only a very small amount of sugar is put out, the threshold is probably in the neighborhood of 0.17 per cent. There is nothing striking about the diuresis. The most marked urine output occurred toward the end of the curve. During the experiment, about 0.04 gm. of sugar is excreted. The curve represented by the dotted line shows the patient's reaction to the same test one month after operation. It is a normal curve. *A*, glucose, 100 gm. in 300 c.c. of water.

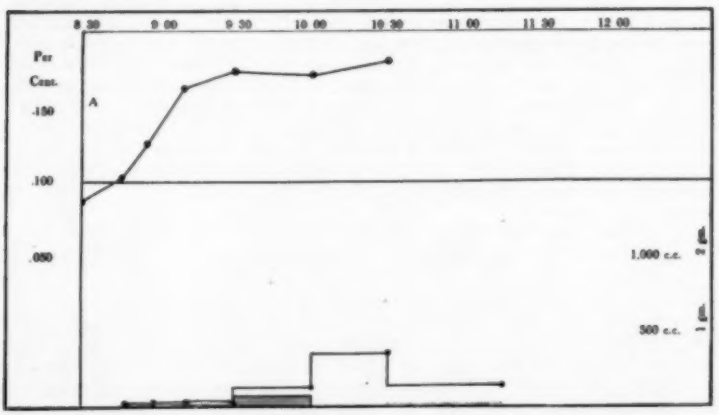

Chart 12 (Case 24).—A diabetic type of reaction in a patient with Graves' disease. The rise is moderately abrupt, the high point being reached in a little less than one hour after the administration of glucose. There is a marked plateau, for the blood sugar shows no tendency to fall two hours after the administration of glucose. The threshold fixed beautifully at about 0.175 per cent. When the blood sugar reaches 0.174 per cent. there is just a trace of sugar in the urine. In the period from 9:30 to 10 o'clock a little more sugar is excreted; so it is altogether probable that after 9:30 the blood sugar went a little higher. In the period from 10 to 10:30, when the blood sugar is between 0.17 per cent. and 0.18 per cent. no sugar is excreted. Following the period when the blood sugar reaches 0.18 per cent. a trace of sugar again appears in the urine. During the period from 10 to 10:30 there is a marked diuresis, which may have obscured a slight trace of sugar. *A*, glucose, 100 gm. in 500 c.c. of water.

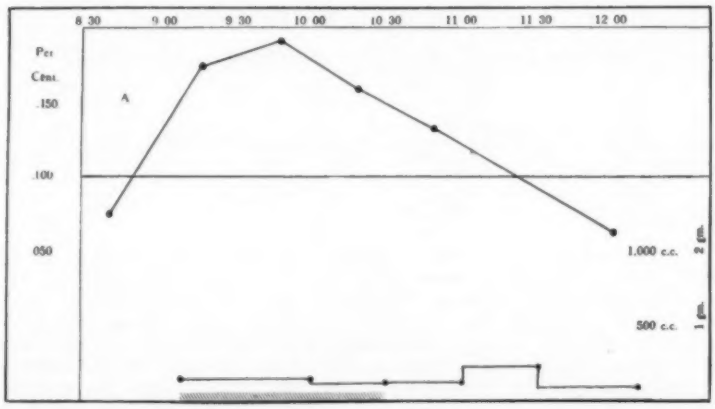

Chart 13 (Case 25).—A slight leaning toward the diabetic type of reaction in a patient with hyperthyroidism. The rise is rather abrupt, the high point being reached one hour after the administration of the glucose. There is no plateau. The fall is rather slow, the whole reaction lasting two and three-quarters hours. The blood sugar reached 0.19 per cent. as the highest point, and only a small amount of sugar is excreted in the urine. The threshold, therefore, both on the rise and on the fall must be somewhere in the neighborhood of 0.18 per cent. There is nothing remarkable about the diuresis. *A*, glucose, 100 gm. in 500 c.c. of water.

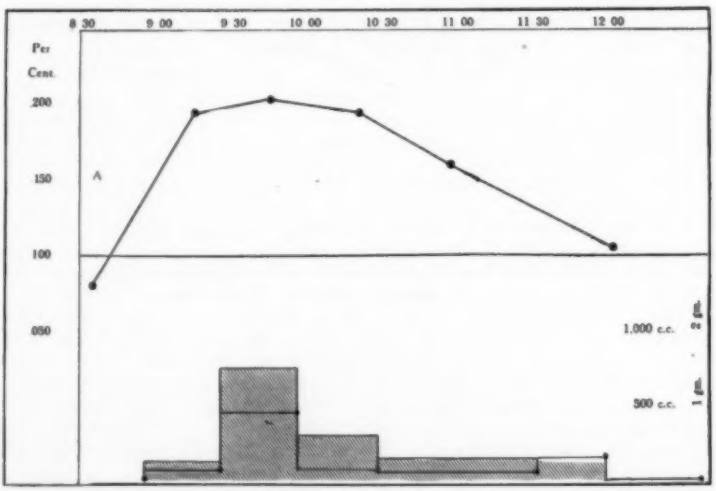

Chart 14 (Case 29).—A diabetic type of reaction in a patient with dyspituitarism. The curve rises rather abruptly, the high point being reached one hour after the ingestion of 100 gm. of glucose. The curve is flattened at the summit and the decline is slow, the whole reaction lasting over three hours. The renal threshold was below 0.19 per cent. on the up-limb; it fell below 0.15 per cent. on the down-limb. There was a marked diuresis during the period of greatest glycosuria. *A*, glucose, 100 gm. in 300 c.c. of water.

TABLE 20.—Protocol of Glucose Tolerance Test in Case 27

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:20	0.096	16	0
8:30	Glucose, 100 gm. in 300 c.c. water		
9:00	0.124	21	0
10:05	0.103	19	0
10:30	0.101	33	0
11:00	0.101	20	0
12:00	0.086	16	0

Case 28 (Hospital No. 38977).—Diagnosis: cerebellar cyst. D. E., W. F. S., aged 16, gave a history of illness which began at 10 years, with headache, followed by gradual loss of vision. The patient was blind for two years. There was frequent vomiting with headache. Convulsions began during the second year of illness, and about the same time the patient began to have difficulty in walking. Additional symptoms were: loss of smell, failure of memory, irritability, marked gain in weight and absence of menstruation. The essential results of examination were: fairly well developed, rather fat; hypertrichosis; head large, suggesting internal hydrocephalus; divergent strabismus; slight ptosis on left; slight nystagmus to left; total blindness due to optic atrophy, and marked ataxia. The roentgen-ray examination revealed entire sella region obscured, probably destroyed, suggesting a growth in that region. There was marked evidence of intracranial pressure. The left cerebellar cyst was evacuated by operation Jan. 25, 1916. The glucose tolerance test was made Jan. 17, 1916. The protocol of this test is given in Table 21.

TABLE 21.—Protocol of Glucose Tolerance Test in Case 28

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
9:20	0.108		
9:25	Glucose, 100 gm. in 300 c.c. water		
9:45	0.126	138	0
10:45	0.171		
10:58	.....	*100	1.79
11:55	0.173		
12:20	.....	50	1.97
12:45	0.126		
4:20	.....	105	0

* Some urine voided involuntarily in bed.

Case 29 (Hospital No. 40109).—Diagnosis: hypophysial tumor; cyst of chiasm. P. R., W. F. S., aged 32, gave a history of symptoms which began two years before admission to the hospital, with difficulty in urination and dull headache. The hands and feet grew larger. Two attacks of sudden blindness occurred with as sudden recovery. On admission, May 4, 1916, examination showed a well nourished woman; face broad, features masculine, maxillary prognathism; marked hypertrichosis; hands broad and fingers short; visual fields constricted; complete bitemporal hemianopsia and infantile pelvic organs. The roentgen-ray examination revealed acromegalia. An operation was performed June 5, 1916, for evacuation of infundibular cyst. The glucose tolerance test was made May 24, 1916. The data of this test are presented in Chart 14.

Case 30 (Dispensary No. 52670).—Diagnosis: paralysis agitans; acromegalia. A. S., W. F. W., aged 60, came for relief of long standing constipation. Examination showed a well nourished woman with tendency to obesity; mask-like expression; muscular rigidity; characteristic tremor of hands; head large; massive features; wide separation of teeth, and spade-like hands. Roentgen-ray examination revealed large sella, thickened skull and phalanges, thickened and tufted. The glucose tolerance test was made March 2, 1916. The data of this test are presented in Chart 15.

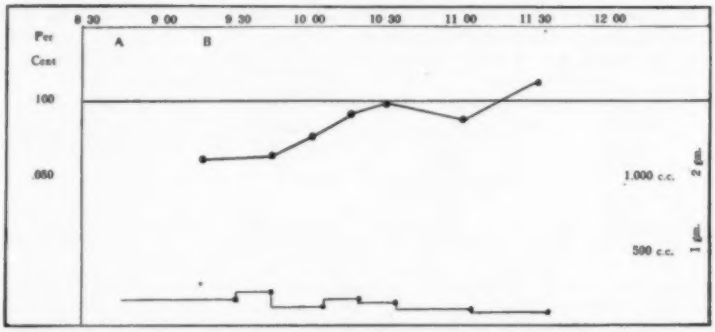

Chart 15 (Case 30).—Increased tolerance for carbohydrate in a patient with dyspituitarism. The blood sugar, to begin with, was quite low. The rise was slow, but after once reaching its high point, this high point was well sustained. There was a gradual elevation of the blood sugar from the time the experiment was begun until it was concluded, a period of two hours. There was a moderate diuresis which gradually fell throughout the experiment. *A*, voided; *B*, glucose, 100 gm. in 300 c.c. of water.

Case 31 (Dispensary No. F. 50445).—Diagnosis: disturbance of endocrine glands (hypophysis (?) interenal body (?)). M. G., W. M. S., aged 18, complained of swelling and cyanosis of hands, most marked in winter. Examination showed a rather short, well nourished but not obese boy; head large, and all features massive; ears large, high placed and standing out prominently; maxillary prognathism; anteroposterior bowing of spine; breasts large, with well developed nipples; absence of axillary hair; scant pubic hair, with transverse arrangement; hypospadia; undescended left testicle and hands greatly enlarged from edema and extremely cyanotic. Roentgen-ray examination revealed periarticular swelling of hands, but no bone changes, enlargement of vessels of anterior skull region and normal sella, although unusual in shape. The glucose tolerance test was made March 20, 1916. The patient fasted. The protocol of this test is given in Table 22. The epinephrin test was made April 17, 1916, the data of which are presented in Chart 22.

TABLE 22.—Protocol of Glucose Tolerance Test in Case 31

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:35	0.109		
8:42	Glucose, 100 gm. in 300 c.c. water		
8:44	.....	70	0
8:55	0.122	921	0
9:10	0.132	632	0
9:30	0.137	960	0
9:49	0.111	677	0
10:27	0.103	246	0
11:28	0.109	135	0

Case 32 (Hospital No. 36128).—Diagnosis: dyspituitarism (?). T. A., W. M. M., aged 38, gave a history of onset of symptoms occurring three years before admission, with a convulsion. Since then convulsions occurred at long intervals. The patient grew dull and morose, and very irritable. There was a rapid gain in weight. The patient was impotent for three years. Examination, July 30, 1916, showed a large, well nourished man with no abnormality other than a mild hypertension of 170:90. The visual fields were normal.

The optic disks were normal. Roentgen-ray examination revealed normal sella. The Wassermann test in blood serum was negative. The glucose tolerance test was made July 7, 1917. The protocol of this test is given in Table 23.

TABLE 23.—Protocol of Glucose Tolerance Test in Case 22

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
9:00	0.100		
9:01	Glucose, 100 gm. in 300 c.c. water		
9:15	0.124		
9:30	0.155	28	0
10:00	0.215	36	0.36
11:00	0.200	68	2.26

SUMMARY

The five patients with obvious hyperthyroidism showed a lowered sugar tolerance. The blood sugar curve has to some extent the high, sustained, prolonged features of the diabetic type. All five had glycosuria, but only one (Case 22) put out a large amount of sugar. Case 26 had only a slight glycosuria, although the blood sugar went above 0.2 per cent. The urine contained albumin and a few hyaline casts, indicating a mild nephritis, no doubt with renal impermeability to glucose. In this patient the sugar tolerance was more seriously disturbed than a study of the urine alone would indicate. Case 23, Chart 11, is of special interest on account of the improved sugar tolerance one month after operation. The young man (Case 27) with a large colloid goiter and no obvious symptoms of disturbed thyroid function gave a normal reaction. The two patients (Cases 28 and 29, Chart 14) with well marked symptoms of overfunction of the hypophysis both yielded typical diabetic types of blood sugar curves. The mildly acromegalic (Case 30, Chart 15) in the quiescent or underfunction stage, had an unusually low fasting blood sugar and only a slight rise after 100 gm. of glucose, indicating a high sugar tolerance. Finally the patients (Cases 31 and 32) with only suggestive symptoms of deranged hypophysial function gave, the one a normal reaction, save for the remarkable diuresis; the other the characteristic reaction of low glucose tolerance.

REACTIONS IN VARIOUS DISEASES

In concluding we wish to report the reactions in a few patients with various disorders. Briefly, the clinical features of each case and the results of the test are as follows:

Case 33 (Hospital No. 35175).—Diagnosis: acute lobar pneumonia; syphilis of the central nervous system. S. R., W. M. S., aged 44, was treated in a psychiatric clinic in the spring of 1915 for paresis. The present illness came on acutely two days before admission, Dec. 14, 1915. It was a typical lobar pneumonia with the crisis on the fourth day. The glucose tolerance test was made Dec. 31, 1915. The protocol of this test is given in Table 24.

TABLE 24.—Protocol of Glucose Tolerance Test in Case 33

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:55	0.101		
8:56	Glucose, 100 gm. in 300 c.c. water		
9:25	0.164	?	0
9:50	0.195	20	Present
10:10	0.172	464	0.1
10:35	0.174	500	0.14
11:10	0.156	340	0.15
12:00	.....	211	0

Case 34 (Dispensary No. F-49930).—Diagnosis: emphysema; chronic bronchitis; asthma. M. E., W. M. M., aged 50, had had a cough, off and on, for fifteen years and dyspnea without definite attacks of asthma. The cough was most marked in late summer and early fall. Examination showed well marked emphysema, with sonorous and sibilant râles. The glucose tolerance test was made Jan. 27, 1916. The data of this test are presented in Chart 16.

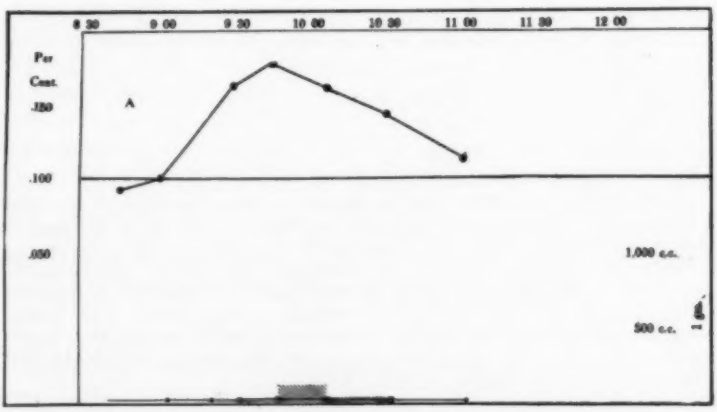

Chart 16 (Case 34).—The blood sugar rise, though relatively high, is fairly rapid, the high point being reached about fifty minutes after the administration of glucose. There is no plateau, and the fall is relatively rapid, the whole reaction being over in about two and one-half hours. The highest blood sugar is 0.178 per cent., and the patient puts out just a very small amount of glucose before this point is reached, so that the threshold on the rise is evidently a little above 0.17 per cent. On the fall the threshold is a little lower, for sugar is put out in the specimen collected at 10:33 and during the period from 10:06 to 10:33 the blood sugar falls from 0.16 to 0.145. There is no marked diuresis. At 6 a. m. the patient voided. *A*, glucose, 100 gm. in 310 c.c. of water.

Case 35 (Hospital No. 35268).—Diagnosis: acute tonsillitis. H. H., W. M. S., aged 16, came to the hospital because sugar had been found in the urine. Except for mild tonsillitis, the boy was otherwise normal. During three weeks' stay in the hospital, sugar was never found in the urine. The glucose tolerance test was made Jan. 24, 1916. The protocol of this test is given in Table 25.

TABLE 25.—Protocol of Glucose Tolerance Test in Case 35

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:45	0.098		
8:46	Glucose, 100 gm. in 300 c.c. water		
9:03	0.124	107	0
9:16	0.146	88	0
9:30	0.172	136	0
9:45	0.178	200	0
10:00	0.182	152	0
10:33	0.176	163	0
11:05	0.141	127	0
11:55	0.144	97	0

Case 36 (Hospital No. 21835).—Diagnosis: chronic pelvic inflammatory disease. E. P., W. F. M., aged 22, entered the gynecologic service of the hospital for a pelvic operation. A small amount of sugar was found in the urine which at once disappeared on dietary restriction and did not reappear on the regular ward diet. The glucose tolerance test was made Jan. 31, 1916. The protocol of this test is given in Table 26.

TABLE 26.—Protocol of Glucose Tolerance Test in Case 36

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:30			
8:35	Glucose, 50 gm. in 200 c.c. water		
9:00	0.132		
9:15	.....	192	0
9:30	0.168		
9:45	.....	220	0
10:00	0.152		
10:15	.....	416	0
10:30	0.098		
10:45	.....	368	0
11:00	0.088		
11:15	.....	380	0

Case 37 (Hospital No. 35436).—Diagnosis: acute rheumatic fever; otitis media; syphilis (Wassermann); chronic tonsillitis. E. W., B. M. S., aged 24, was in the hospital with acute rheumatic fever in January, 1916. There was a return of symptoms shortly after discharge. The patient was readmitted Feb. 2, 1916. Physical examination disclosed pyorrhea alveolaris; chronic tonsillitis; genital scar, and swelling and redness of many joints. The Wassermann reaction was ++++. The patient made a rapid recovery after administration of salicylates. The glucose tolerance test was made Feb. 14, 1916. The protocol of this test is given in Table 27.

TABLE 27.—Protocol of Glucose Tolerance Test in Case 37

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
6:30	*Breakfast		
8:35	0.098	122	0
8:52	Glucose, 100 gm. in 300 c.c. water		
9:20	0.111	92	0
9:40	0.114	66	0
10:00	0.109		
10:20	0.095	68	0
11:05	0.096	49	0

*Small piece toast, small piece butter, oatmeal with sugar.

SUMMARY

The patient with general paresis (Case 33) convalescing from pneumonia, and the patient (Case 34, Chart 16) with asthma, showed a moderate decrease in carbohydrate tolerance; both excreted a little sugar after the administration of 100 gm. of glucose. The patient (Case 35) sent into the hospital as a diabetic on account of occasional glycosuria, showed a rather high and a definitely prolonged reaction without glycosuria. The test suggested only a little disturbance of sugar tolerance, and even on a very liberal general diet the patient never had glycosuria while in the hospital. The patient (Case 36) from the gynecologic service was investigated also on account of transient glycosuria. Except for being somewhat high, the curve is otherwise normal, and subsequently sugar was not again found. The patient (Case 37) with rheumatic fever was having an afternoon elevation of temperature up to 101 at the time the test was made; he had only a very slight rise of blood sugar after taking 100 gm. of glucose.

II

Epinephrin Hyperglycemia

Our knowledge of the effects of epinephrin on carbohydrate metabolism in man has been gained chiefly from studies on epinephrin glycosuria. There are available only scant data about its effect on blood sugar and these data consist of single blood sugar determinations or at most of a few determinations at irregular intervals.[8] Out studies with epinephrin were begun to discover the renal threshold for glucose in normal persons, and were then extended to confirm some interesting preliminary observations. The method employed was to give 50 gm. of glucose in the morning after the night fast and to follow this in from one-half to one hour with a subcutaneous injection of from 0.66 mg. to 1 mg. of epinephrin. The blood sugar, the blood pressure, the diuresis, the glycosuria and the general symptoms were studied at short intervals after the injection.

EPINEPHRIN REACTION IN NORMAL PERSONS

We have records of the epinephrin reaction in seven healthy persons (Case 1, Chart 17; Case 2, Chart 18; Case 3; Case 38, Chart 19; Case 40, Chart 23; Case 41, Chart 26). Data pertaining to Cases 1, 2 and 3 have already been given; those pertaining to Cases 38, 39, 40 and 41 are briefly as follows:

Case 38.—S. W., W. M. M., healthy physician, aged 35, was given the epinephrin test Nov. 19, 1915. The data of this test are presented in Chart 19. There was a moderate general reaction; some palpitation and throbbing.

8. Bang: Der Blutzucker, Weisbaden, 1913, p. 85. Landau: Ztschr. f. klin. Med., 1914, **79**, 201.

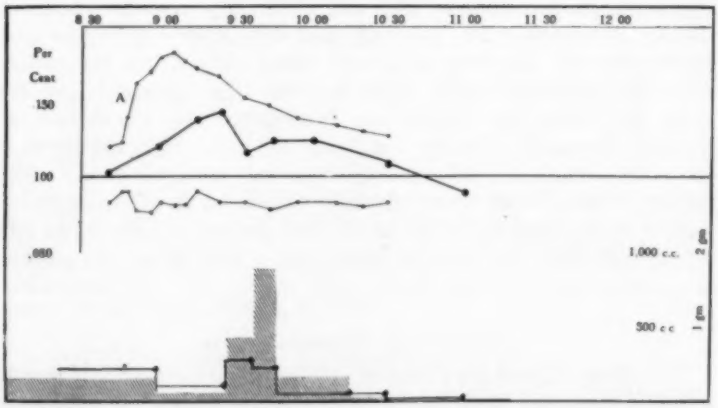

Chart 17 (Case 1).—A normal blood sugar reaction after epinephrin, with a low renal threshold. This chart offered much difficulty in interpretation, because the urine passed shortly after the administration of epinephrin, when the blood sugar was 0.12 per cent., showed more sugar than the following specimen collected during the period when the blood sugar rose from 0.12 per cent. to 0.14 per cent. The only possible explanation was that the patient had had alimentary glycosuria after the administration of 50 gm. of glucose. For this reason he was tested by administering 50 gm. of glucose on an empty stomach, and glycosuria did occur. As the chart shows, the renal threshold is very low; it is certainly below 0.14 per cent. and in all probability in the neighborhood of 0.13 per cent. on the rise. When sugar excretion is started the threshold drops off still further, so that the patient continues to put out sugar, even when the blood sugar has fallen down to 0.108 per cent. The rise in the curve is rapid, the highest point being reached forty minutes after the administration of epinephrin. There is practically no plateau, for the blood sugar then rapidly falls off and has reached its original level after two hours and fifteen minutes. There is a well marked diuresis during the period of glycosuria, which again quickly subsides. During the period of the experiment 1.3 gm. of sugar are excreted. The blood pressure reaction is moderate. Patient complained of moderate throbbing and palpitation. At 7:15 a. m. the patient received 50 gm. of glucose in 500 c.c. of water. *A*, epinephrin, 1 mg.

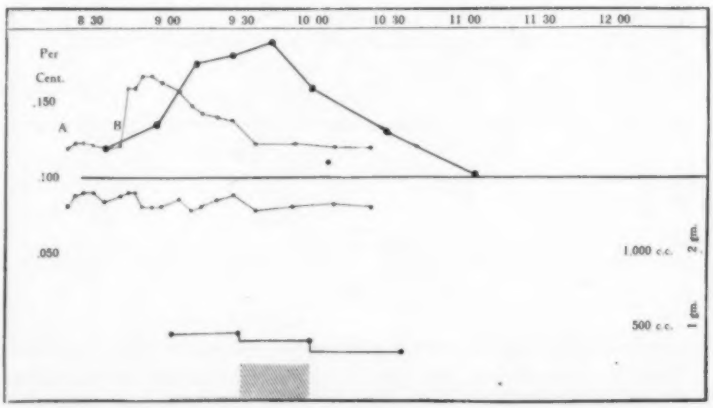

Chart 18 (Case 2).—An epinephrin reaction in a normal person. The blood sugar curve rises rapidly, the high point being reached an hour after the administration of epinephrin. There is no plateau. The blood sugar falls off abruptly from the high point and the whole reaction is over in a little less than two hours. The specimen of urine collected two minutes after the blood sugar reached 0.182 per cent. contains just a trace of sugar. The renal threshold, therefore, is a little below 0.18 per cent. There is nothing remarkable about the diuresis. During the period of the experiment 0.23 gm. of glucose is excreted. Marked subjective symptoms after the administration of epinephrin; marked throbbing and palpitation. The heart action extremely irregular due to numerous premature beats. Patient complained also of dryness of the mouth. At 7:30 a. m. the patient received 50 gm. of glucose in 1,000 c.c. of water. *A*, atropin, 1/60 grain; *B*, epinephrin, 1 mg.

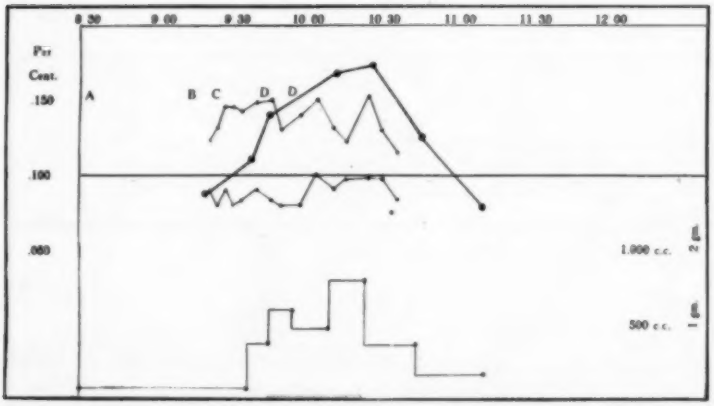

Chart 19 (Case 38).—A characteristic epinephrin reaction with moderate blood pressure and moderate blood sugar reaction. The blood sugar curve rises rapidly, the highest point being reached about thirty minutes after the administration of the epinephrin. There is no plateau. The blood sugar falls rapidly, and the whole reaction is over in less than two hours. It would appear that the threshold on the up-curve is somewhere between 0.14 per cent. and 0.15 per cent.; however, on the down-curve no sugar is excreted after the blood sugar has reached 0.173 per cent. Therefore, it is altogether probable that on the rise the blood sugar must have mounted to a higher point than is indicated on the chart during the interval between the specimens taken at 9:46 and 10:11. Therefore, the threshold is between 0.17 per cent. and 0.18 per cent. The diuresis is extremely marked. It is true the patient did drink some water in the early part of the experiment, but this would hardly account for the whole of the marked diuresis. The patient excreted only traces of sugar. Following the administration of epinephrin the patient complained of disagreeable throbbing in the abdomen and in the vessels of the neck. *A*, glucose, 50 gm. in 500 c.c. of water; *B*, water, 240 c.c.; *C*, epinephrin, 1 mg.; *D*, water, 120 c.c.

CASE 39.—D. T. B., W. M. S., healthy medical student, aged 24, was given the epinephrin test, June 15, 1916, the atropin-epinephrin test, June 16, 1916, and the pilocarpin-epinephrin test, June 18, 1916. The protocols of these tests are given in Tables 28, 29 and 30, respectively.

TABLE 28.—PROTOCOL OF EPINEPHRIN TEST IN CASE 39

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:30	Glucose, 50 gm. in 300 c.c. water		
9:00	0.135	60	0
9:02	Epinephrin, 0.66 mg.		
9:20	0.195	420	Trace
10:00	0.205	750	1.72
10:30	0.146	192	1.05
11:00	0.103	90	0
11:30	0.092	50	0

TABLE 29.—PROTOCOL OF ATROPIN-EPINEPHRIN TEST IN CASE 39

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:30	Glucose, 50 gm. in 300 c.c. water		
8:45	Atropin, 1/60 gr.		
9:00	0.102	60	0
9:02	Epinephrin, 0.66 mg.		
9:30	0.124	116	0
10:00	0.115	580	0
10:30	0.095	120	0
11:00	0.090	98	0
11:30	0.086	78	0

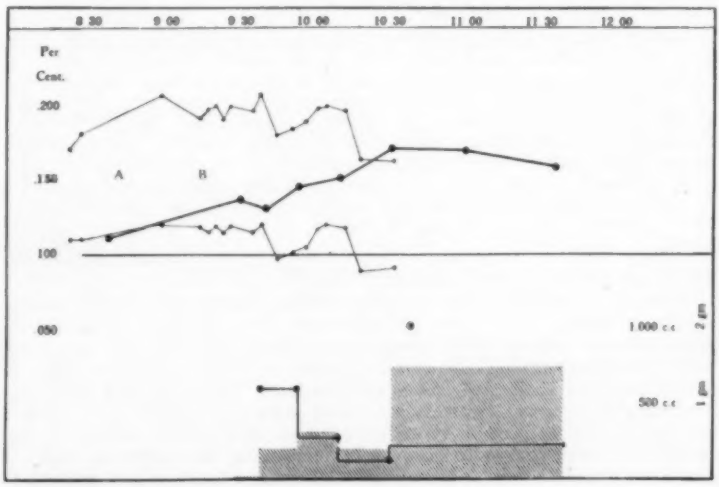

Chart 20 (Case 12).—A characteristic diabetic blood sugar chart, following the administration of epinephrin. The rise is slow, the highest point being reached one hour and fifteen minutes after the administration of epinephrin. The plateau is sustained. The blood sugar is just beginning to drop two hours and twenty minutes after the administration of epinephrin. The threshold on the rise is fixed accurately at 0.14 per cent. There is an initial or early diuresis following the administration of epinephrin; but during the period of glycosuria the diuresis rapidly falls. The total sugar excretion cannot be estimated because the experiment was broken off during the period of most marked glycosuria. The patient had moderate hypertension, and there is only a slight blood pressure reaction following the epinephrin. The initial rise of blood pressure followed catheterization undertaken to facilitate the collection of urine specimens. At 6:30 a. m. the patient received a carbohydrate free breakfast. *A*, water, 300 c.c.; *B*, epinephrin, 10 mg.

TABLE 30.—Protocol of Pilocarpin-Epinephrin Test in Case 30

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:28	Glucose, 50 gm. in 300 c.c. water		
8:45	Pilocarpin, 1/10 gr.		
9:00	0.131	72	0
9:02	Epinephrin, 0.66 mg.		
9:30	0.160	240	0
10:00	0.172	430	0
10:30	0.140	144	0
11:00	0.112	72	0
11:30	0.092	40	0

Case 40.—A. H. B., W. M. S., healthy medical student, aged 23, was given the epinephrin test, June 21; the atropin-epinephrin test, June 22, and the pilocarpin-epinephrin test, June 23, 1916. The data of these tests are presented in Charts 23, 24 and 25, respectively.

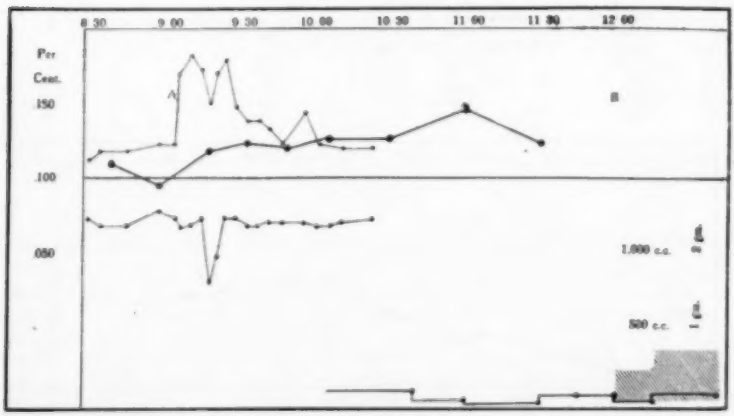

Chart 21 (Case 24).—This chart is a striking contrast to Chart 6, portraying the alimentary test in the same patient. Although there is an extreme blood pressure reaction after epinephrin, the blood sugar does not rise as high as in the alimentary test. However, although the blood sugar rises only moderately and very slowly, the rise is well sustained. Two and a half hours after the administration of epinephrin the blood sugar has not yet come down to its original level. There is no diuresis; indeed, only a small amount of urine is excreted, a much smaller amount than following the alimentary test. At noon the patient ate his luncheon, and following this there is a marked alimentary glycosuria. As stated above, the blood pressure reaction after epinephrin was extreme. The patient was blanched, and after an attempt to pass urine the diastolic pressure fell to 30 mm. Hg. The patient almost fainted at this time; but it was remarked that in spite of his extreme pallor and faintness there was no sweating. At 8 a. m. the patient received 50 gm. of glucose in 500 c.c. of water; at 8:10 a. m., voided. *A*, epinephrin, 1 mg.; *B*, luncheon.

Case 41.—N. B. H., W. M. S., healthy medical student, aged 23, was given the epinephrin test, June 28; the atropin-epinephrin test, June 29, and the pilocarpin-epinephrin test, June 30, 1916. The data of these tests are presented in Charts 26, 27 and 28, respectively.

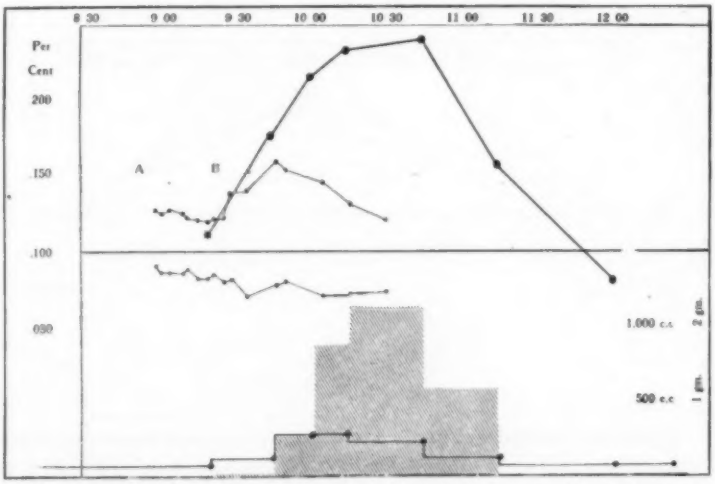

Chart 22 (Case 31).—A rather marked epinephrin reaction in a patient with symptoms suggesting dyspituitarism. The blood sugar rises rapidly, the high point being reached eighty minutes after administration of the epinephrin. The fall is still more abrupt, the whole reaction lasting about two hours. A bare trace of sugar is excreted in the specimen collected immediately after the blood sugar has reached 0.176 per cent. Therefore, the renal threshold is a little over 0.17 per cent. During the period of the experiment 3.7 gm. of glucose were excreted. There is moderate diuresis during the period of glycosuria. There is a moderate blood pressure reaction, but the patient complained of no unpleasant symptoms during the test, although moderate throbbing in the vessels was apparent. The heart's action showed marked sinus arrhythmia. At 7 a. m. the patient voided. *A*, glucose, 50 gm. in 300 c.c. of water; *B*, epinephrin, 1 mg.

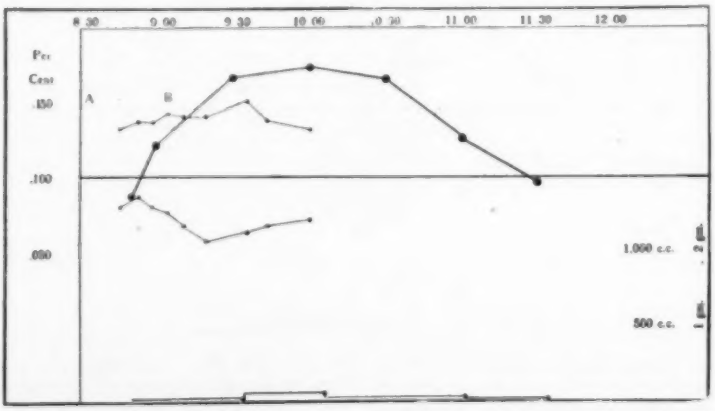

Chart 23 (Case 40).—Reaction after epinephrin. *A*, glucose, 50 gm. in 300 c.c. of water; *B*, epinephrin, 0.66 mg.

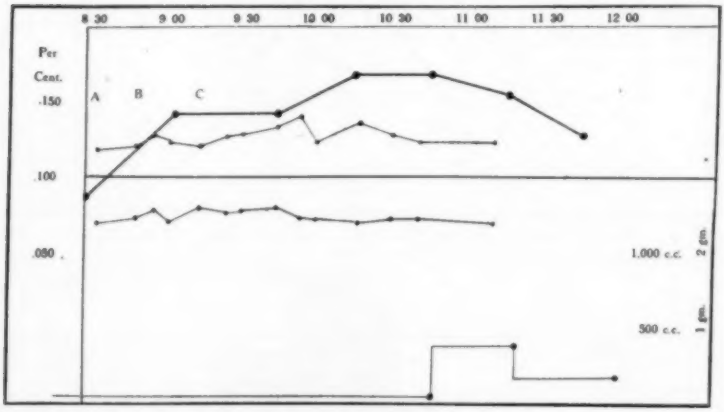

Chart 24 (Case 40).—Reaction after atropin and epinephrin. At 7:50 a. m. the patient voided. A, glucose, 50 gm. in 300 c.c. of water; B, atropin, 1/60 grain; C, epinephrin, 0.66 mg.

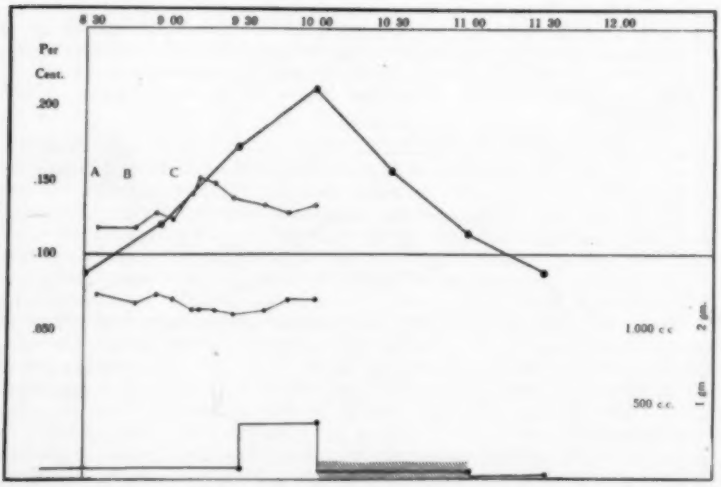

Chart 25 (Case 40).—Reaction after pilocarpin and epinephrin. At 7:50 a. m. the patient voided. *A*, glucose, 50 gm. in 300 c.c. of water; *B*, pilocarpin, 1/10 grain; *C*, epinephrin, 0.66 mg.

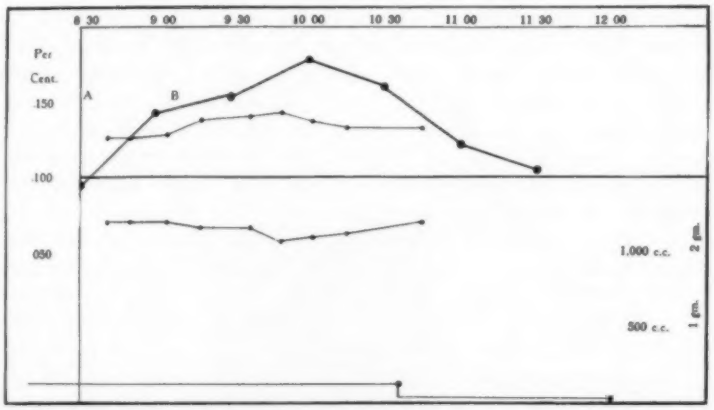

Chart 26 (Case 41).—Reaction after epinephrin. At 7:10 a. m. the patient voided. *A*, glucose, 50 gm. in 300 c.c. of water; *B*, epinephrin, 0.66 mg.

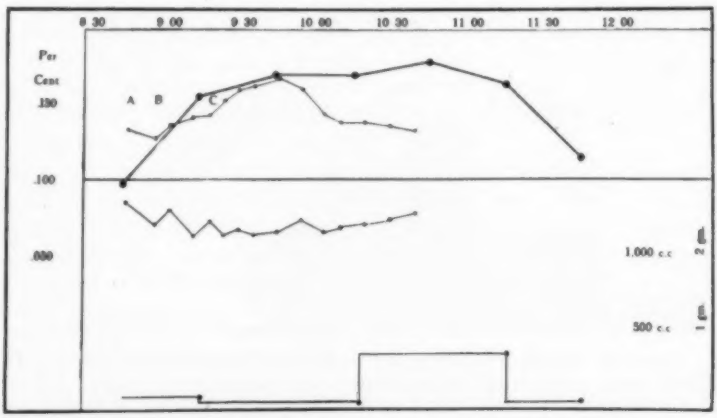

Chart 27 (Case 41).—Reaction after atropin and epinephrin. At 7:10 a. m. the patient voided. *A*, glucose, 50 gm. in 300 c.c. of water; *B*, atropin, 1/100 grain; *C*, epinephrin, 0.60 mg.

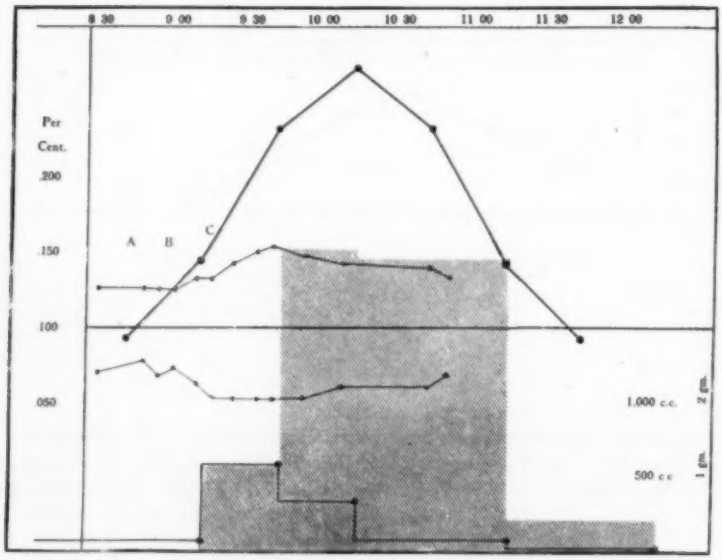

Chart 28 (Case 41).—Reaction after pilocarpin and epinephrin. At 7:15 a. m. the patient voided. *A*, glucose, 50 gm. in 300 c.c. of water; *B*, pilocarpin, 1/10 grain; *C*, epinephrin, 0.66 mg.

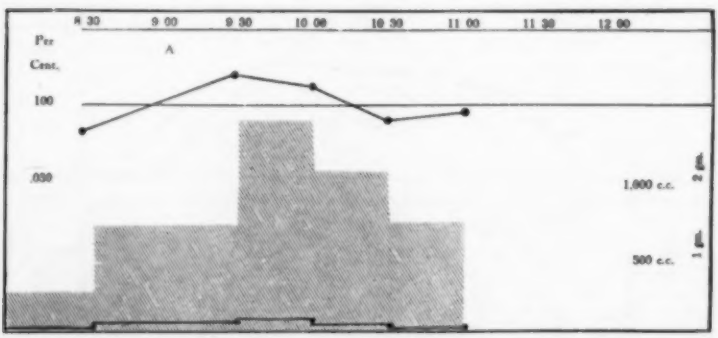

Chart 29.—Reaction in an unusually well marked case of renal diabetes. The blood sugar curve is altogether normal, the highest point, namely, 0.12 per cent., being reached within thirty minutes after taking 100 gm. of glucose, and the whole reaction being over in an hour and a half. However, there is a marked glycosuria in spite of the normal blood sugar curve. When the experiment was begun after the night fast the patient had considerable sugar in the urine, although the blood sugar was only 0.084 per cent. At 6 p. m. the patient had dinner; at 9 p. m., ate an ice cream cone, and at 8 a. m., voided. *A*, glucose, 100 gm. in 300 c.c. of water.

SUMMARY

Following the subcutaneous administration of epinephrin to normal persons, there was a prompt rise in the blood sugar, which reached its maximum in one hour and then rapidly subsided, the whole reaction being over in two hours. Sometimes the rise was a little quicker; sometimes it occurred somewhat more slowly, but the variations are small. Four persons receiving 1 mg. of epinephrin all had glycosuria varying from a trace of sugar to an excretion at the rate of 7.9 gm. per hour (Case 3). Of the three receiving 0.66 mg. of epinephrin only one had glycosuria. The occurrence of glycosuria and its degree ran parallel with the degree of hyperglycemia. The apparent exception to this statement (Chart 17) is interesting because this person, although normal in all other respects, had a low renal threshold. The threshold was low to the alimentary test as well as after epinephrin. All of our observations show that epinephrin has no influence on the renal threshold. The five persons with glycosuria had a more or less marked diuresis occurring principally during the period of sugar excretion. However, the diuresis was not always parallel with the glycosuria and as further observations showed there was sometimes a marked diuresis without glycosuria and sometimes a falling diuresis during the period of most marked glycosuria. Two of the patients with glycosuria (Cases 2 and 3) had previously had alimentary tests and neither gave unusual reactions; indeed, Case 3 showed only a slight rise in the blood sugar after 100 gm. of glucose, whereas, after epinephrin he had an extreme hyperglycemia and glycosuria. There was no correspondence whatsoever between alimentary hyperglycemia and epinephrin hyperglycemia. All seven persons had a mild or a moderately severe blood pressure reaction and the general symptoms ran parallel with the degree of blood pressure response, consisting of unpleasant palpitation and throbbing, of a little nervousness and headache, and in one instance also of chilliness and blanching of the skin. There is no correspondence between the degree of blood pressure response or the severity of the general symptoms and the degree of hyperglycemia. As we shall later show, atropin often greatly increases the blood pressure effect of epinephrin, whereas the hyperglycemia is thereby diminished.

EPINEPHRIN REACTIONS IN VARIOUS DISEASES

We have studied the epinephrin reaction in various diseases and state briefly the main clinical features and the results of the test in those cases not already cited (Case 12, Chart 20; Case 24, Chart 21; Case 31, Chart 22; Cases 42, 43, 44 and 45).

CASE 42 (Hospital No. 34891).—Diagnosis: acute rheumatic fever. A. S., W. M. M., aged 33, gave a history of three previous hospital admissions for

acute rheumatic fever. The patient was otherwise healthy, except that he had always been a nervous man. The present admission, March 4, 1915, was for another attack of rheumatism. The patient had a mild attack without complications. The epinephrin test was made Nov. 15, 1915. The protocol of this test is given in Table 31.

TABLE 31.—Protocol of Epinephrin Test in Case 42

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
8:45	0.085		
	Glucose, 50 gm. in		
8:45	400 c.c. water		
9:15	0.101		
9:30	0.092		
9:32	Epinephrin, 1 mg.		
9:45	0.137	900	0
10:05	0.182	408	0.53
10:25	0.218	90	2.16
10:45	0.209		
11:00	.....	208	1.0
11:15	0.150	1350	0

Case 43 (Hospital No. 34996).—Diagnosis: syphilis; syphilitic periostitis; secondary anemia. J. H., B. M. S., aged 25, gave a history of irregular general symptoms for eight months; headache, general pains and weakness. Examination on admission to the hospital Nov. 8, 1915, showed general glandular enlargement, points of tenderness over elbow, ribs and cervical and lumbar spines. The Wassermann reaction was ++++. The epinephrin test was made Dec. 8, 1915. The protocol of this test is given in Table 32.

TABLE 32.—Protocol of Epinephrin Test in Case 43

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
7:30	Glucose, 50 gm.		
8:45	0.098		
9:13	Epinephrin, 1 mg.		
9:29	0.117	50	0
9:45	0.128	90	0
9:58	0.146	162	0
10:15	0.141	90	0
10:45	0.119	250	0
11:15	0.120	50	0

Case 44 (Hospital No. 34983).—Diagnosis: carcinoma of prostate; cystitis; myocardial insufficiency; carcinoma of bones (metastases); acute fibrinous pleurisy; acute fibrinous pericarditis. P. N., B. M. M., aged 57, had a sharp pain in lower back in April, 1915. Soon after the patient had difficulty in walking; frequent urination and difficulty in urination, and edema of the legs. On admission to the hospital, examination showed emaciation; anemia; cardiac enlargement; retention of urine; firm, hard prostate and metastases in bones. The phenolsulphonephthalein test was 64 per cent. There was a gradual downward course, ending in death, April 20, 1916. The anatomic diagnosis was essentially the same as the clinical. The epinephrin test was made Feb. 7, 1916. The protocol of this test is given in Table 33.

TABLE 33.—Protocol of Epinephrin Test in Case 44

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
9:00	0.100		
	Glucose, 50 gm. in		
9:06	150 c.c. water		
9:30	0.108	28	0
9:32	Epinephrin, 1 mg.		
9:45	0.170	26	0
10:02	0.195	180	0
10:15	0.210	4	0
10:30	0.205	6	0
10:48	0.149	25	0
11:00	0.141	125	0
11:58	0.117	37	0

CASE 45 (Hospital No. 35928).—Diagnosis: tuberculous peritonitis; pleurisy with effusion. L. J., B. M. S., gave a history of onset of symptoms in April, 1915, with pleurisy. A second attack of pleurisy occurred in June, 1915. The patient was well till December, 1915, when pleurisy came on again, followed by swelling of abdomen, loss of appetite and loss of weight. On admission to the hospital, Feb. 1, 1916, examination showed a poorly nourished colored man with considerable fever, pleurisy on both sides with effusion on right, ascites and epigastric mass. There was a gradual loss of fever and improvement in general condition. The epinephrin test was made Feb. 28, 1916. The protocol of this test is given in Table 34. The blood pressure rose from 122 and 78 to 178 and 86. The patient showed restlessness, palpitation and extrasystolic irregularity.

TABLE 34.—PROTOCOL OF EPINEPHRIN TEST IN CASE 45

Hour	Blood Sugar, Per Cent.	Urine Volume, C.c. Per Hour	Urine Sugar, Gm. Per Hour
6:00	Light breakfast		
7:30	Glucose, 50 gm. in 200 c.c. water		
8:52	0.081	145	0
9:09	Epinephrin, 1 mg.		
9:28	0.079	269	0
9:50	0.130	93	0
10:10	0.112	42	0
10:30	0.100	57	0
11:00	0.077	88	0
11:35	0.078	79	0

SUMMARY

In a general way these epinephrin reactions show the same features as were commented on in discussing the reaction in normal persons. Only two of the reactions deserve special consideration. However, a few differences may be pointed out. Case 31, Chart 22, is noteworthy on account of the well marked diuresis which, however, was not so marked as after the alimentary test even though following the alimentary test there was no glycosuria. The disproportion between the moderate blood sugar reaction after the alimentary test and the marked hyperglycemia and glycosuria after epinephrin also deserve attention. Case 42 is unusual in showing a falling diuresis during the period of most marked glycosuria. Case 44 had carcinoma of the prostate and urinary retention and showed, as was to be expected, renal impermeability; although the blood sugar rose to 0.21 per cent. only a trace of sugar appeared in the urine. Cases 43 and 45 are remarkable only on account of the slight blood sugar rise after 1 mg. of epinephrin. Both patients were colored men, and from our limited experience we are inclined to believe that the colored race shows less carbohydrate metabolism disturbance after epinephrin than does the white race.

The two epinephrin reactions deserving special comment are the reaction in a diabetic (Case 12, Chart 20) and the reaction in a patient with hyperthyroidism (Case 24, Chart 21). In the previous section we described the fundamental difference between the normal type and the diabetic type of reactions to the alimentary test. Both of these patients responded to the alimentary test with a high and very pro-

longed blood sugar curve, one (Case 12, Chart 5) with a low renal threshold, the other (Case 24, Chart 12) with a normal renal threshold. The important point we wish to emphasize now is that after epinephrin the same prolonged blood sugar curve was reproduced. The diabetic with a low renal threshold put out a large amount of sugar in the urine. The patient with hyperthyroidism and a normal renal threshold had less hyperglycemia after epinephrin than after the alimentary test, and since the blood sugar rose only to 0.15 per cent. no sugar flowed off in the urine. However, the alimentary hyperglycemia following luncheon, added to the epinephrin hyperglycemia, is followed by glycosuria. On an ordinary diet the patient never had sugar in the urine. The extreme blood pressure reaction, the marked cardiac irregularity and the severe general symptoms following epinephrin are also noteworthy.

EFFECTS OF ATROPIN AND PILOCARPIN ON EPINEPHRIN HYPERGLYCEMIA

Falta, Newburgh and Nobel[9] state that atropin increases the glycosuric effect of epinephrin, whereas pilocarpin decreases it. Of four persons who had no glycosuria after the injection of epinephrin three became positive when the second injection was preceded by giving atropin for a few days. Two cases with glycosuria after epinephrin became negative when the second injection was preceded one-half hour by an injection of pilocarpin. These results fit in so well with the general facts established for the antagonistic action of autonomic and sympathetic nerves on smooth muscle and glands that we had no thought of questioning their correctness. The few preliminary observations we wish to report were made with the confident expectation that they would confirm in a striking way the results reported by Falta, Newburgh and Nobel. We were surprised to find that, according to our experiments, the facts are directly opposed to their assertions; for atropin, when it acts at all, diminishes the glycosuric effect of epinephrin, and pilocarpin, when it shows any decided influence, increases the glycosuric effect of epinephrin. Had we been better informed, our confidence might have been less complete and our results not so unexpected. Frank and Isaak[10] were unable to confirm in dogs the observations made by Falta, Newburgh and Nobel in man. Doyon and Gautier[11] have shown that an injection of epinephrin causes a marked diminution in the glycogen content of the liver, and that this effect is greatly diminished if the epinephrin is preceded by an injec-

9. Falta, Newburgh and Nobel: Ztschr. f. klin. Med., 1911, **72**, 97.
10. Frank and Isaak: Ztschr. f. exper. Path. u. Therap., 1910, **7**, 326.
11. Doyon and Gautier: Compt. rend. Soc. de biol., 1908, p. 866.

tion of atropin into the bile duct. Doyon and Kareff[12] find that the injection of pilocarpin into a mesenteric vein causes a marked diminution in the glycogen content of the liver. Cavazzani and Soldaini[13] conclude from their experiments that atropin paralyzes the nerves that stimulate the production of glycogen. From clinical observations, Rudisch[14] is convinced that atropin diminishes the tendency to glycosuria in diabetes and he has warmly advocated the use of atropin in this disease. However, Mosenthal[15] was unable to confirm his results.

Our observations on the effects of atropin and pilocarpin on epinephrin hyperglycemia are recorded in Case 2, Chart 18; Case 39; Case 40, Charts 23, 24 and 25; Case 41, Charts 26, 27 and 28.

In Case 2 following epinephrin the blood sugar rose to 0.174 per cent. and is accompanied by marked glycosuria, over 2 gm. of sugar being excreted during the experiment; in a second experiment when the epinephrin is preceded twenty minutes by the subcutaneous injection of atropin, 1/60 grain, the blood sugar rose to 0.19 per cent., but only a small amount of sugar, namely, 0.23 gm. came out in the urine. The discrepancy here between blood sugar and urine sugar would lead one to conclude that there had been a singular variation in renal permeability. However, a simpler explanation is quite likely to be the correct one. The first experiment is one of the earliest in our series, done when we were just beginning to use the Lewis-Benedict blood sugar method. After we became more experienced we discovered that our earlier readings were uniformly too low, due, we are sure, to insufficient or improper heating. The second experiment was done nearly six weeks after the first, at which time we had gained skill and assurance in our blood sugar technic. Therefore we believe that in this instance the urine sugars are more reliable than the blood sugars, and judged by this standard epinephrin alone had a greater effect on sugar mobilization than atropin and epinephrin together. This result is all the more striking when contrasted with the vascular reaction. Following epinephrin alone there was only a moderate blood pressure elevation and moderate palpitation and throbbing; after atropin and epinephrin the blood pressure reaction was twice as marked as after epinephrin alone, and the heart's action was very irregular from numerous premature beats accompanied by disagreeable palpitation and throbbing.

In the other three experiments smaller doses of epinephrin were employed than in Case 2, in order to avoid the unpleasant circulatory

12. Doyon and Kareff: Compt. rend. Soc. de biol., 1908, p. 1056.
13. Cavazzani and Soldaini: Cited by Meyer and Gottlieb, Pharmakologie, 1911, p. 373.
14. Rudisch: Jour. Am. Med. Assn., 1909, **53**, 1366.
15. Mosenthal: Jour. Am. Med. Assn., 1912, **58**, 777.

symptoms that come after the use of atropin and epinephrin. The blood pressure reactions, therefore, do not stand out so prominently, but the blood sugar reactions are all the more striking.

In Case 39, after epinephrin the blood sugar went to 0.205 per cent. and considerable sugar was excreted in the urine; after atropin and epinephrin the blood sugar went only to 0.124 per cent. and no sugar appeared in the urine; after pilocarpin and epinephrin the blood sugar went to 0.172 per cent. without accompanying glycosuria. In this experiment epinephrin alone produced a more marked hyperglycemia than did epinephrin preceded by either atropin or pilocarpin; however, atropin diminished the epinephrin action far more than did pilocarpin.

The results in Cases 40 and 41 are portrayed in the accompanying charts, and need little further comment. In Case 40, after epinephrin alone the blood sugar went to 0.174 per cent. without glycosuria; after atropin and epinephrin to 0.168 per cent without glycosuria; after pilocarpin and epinephrin to 0.21 per cent. with moderate glycosuria.

In Case 41, after epinephrin alone the blood sugar went to 0.178 per cent. without glycosuria; after atropin and epinephrin to 0.178 per cent. without glycosuria; after pilocarpin and epinephrin to 0.272 per cent. with marked glycosuria.

III

The Renal Threshold for Glucose

In making the studies reported in the two previous sections, we had as an important object the determination of the renal threshold for glucose. The data there recorded provides the basis for this section as well, and many of the charts were introduced mainly to illustrate the lessons we wish now to draw from them.

In spite of the importance of the question, no systematic studies of the renal threshold for glucose have been made. Such information as we possess rests mainly on a single blood sugar estimation, or at most on a few estimations at long intervals. For instance, one hour after the administration of glucose, or after the injection of epinephrin, a blood sugar estimation is made, and from this single observation the conclusion is drawn that that particular person does or does not excrete sugar at this level of blood sugar concentration. In this way it has been found that some healthy persons excrete abundant sugar with a blood sugar of 0.11 per cent.[16] while others show no glycosuria with a blood sugar of 0.16 per cent. Since we now know that the blood sugar undergoes marked and rapid fluctuation after the ingestion of carbohydrate, after the administration of epinephrin, and after other procedures that influence its level, we

16. Liefman and Stern: Biochem. Ztschr., 1906, **1**, 299.

realize that single blood sugar observations will only occasionally hit on the highest point of concentration.

However, in spite of the inadequacy of our information there has been ground enough for the prevalent opinion that the renal threshold is a variable factor. In nephritis, for instance, the renal permeability for glucose is often raised, and this alteration has been made the basis of a renal function test; in certain unusual instances of glycosuria spoken of as renal diabetes all the clinical symptoms are thought to depend on a decided lowering of the renal threshold; in diabetes the renal threshold is very inconstant, for many patients have glycosuria when the blood sugar is below 0.15 per cent., whereas others are

TABLE 35.—THE RENAL THRESHOLD IN CASES 1 TO 42, INCLUSIVE

Case Number	Age	Diagnosis	Renal Threshold, Per Cent.	Remarks
1	27	Normal	0.13 to 0.14	
	27	Normal	0.12 to 0.14	Epinephrin, Chart 17
2	33	Normal	0.16 to 0.17	
	33	Normal	0.17 to 0.18	Epinephrin, Chart 18
5	25	Normal	0.13 to 0.14	Chart 2
38	36	Normal	0.17 to 0.18	Epinephrin, Chart 19
7	40	Diabetes, mild	0.15 to 0.20	Chart 3
8	52	Diabetes, mild	0.17 to 0.20	
9	46	Diabetes, mild	0.17 to 0.19	Chart 4
10		Diabetes, inild	0.168 to 0.182	
11	25	Diabetes, moderately severe	0.13 to 0.15	
12	61	Diabetes, moderately severe	0.13 to 0.16	Chart 5
	61	Diabetes, moderately severe	0.13 to 0.15	Epinephrin, Chart 20
13	33	Diabetes, moderately severe	0.17 to 0.20	
	33	Diabetes, moderately severe	0.17 to 0.18	Chart 16
14	39	Diabetes, severe	0.14 to 0.15	Chart 7
15	23	Diabetes, severe	0.178 to 0.182	Chart 8
16	49	Chronic diffuse nephritis	0.20 to 0.205	Chart 9
18	45	Chronic diffuse nephritis	0.17 to 0.18	Chart 10
44	57	Chronic diffuse nephritis	0.20 to 0.21	
23	52	Hyperthyroidism	0.16 to 0.176	Chart 11
24	17	Hyperthyroidism	0.17 to 0.18	Chart 12
25	31	Hyperthyroidism	0.168 to 0.185	Chart 13
26	51	Hyperthyroidism	0.19 to 0.20	
31	18	Dyspituitarism	0.17 to 0.176	Epinephrin, Chart 22
33	44	Lobar pneumonia, convalescent	0.175 to 0.19	
34	50	Bronchial asthma	0.17 to 0.18	Chart 16
42	27	Acute rheumatic fever	0.16 to 0.19	Epinephrin

sugar free, or nearly so, with a blood sugar of 0.5 per cent. and over. These general facts have been known for a long time, but there are no detailed studies of the renal threshold in normal persons with which to compare the alterations produced by disease. As far as we know, only the observations of Jacobsen throw light on the subject. Jacobsen fed thirteen healthy persons 100 gm. of glucose, and at a second test 150 gm. of bread, and estimated the blood sugar at frequent intervals during the following two hours. None of those whose blood sugar remained below 0.16 per cent. had sugar in the urine, whereas, all but one of those whose blood sugar went above 0.17 per cent. did have glycosuria. He concludes, therefore, that in healthy persons the renal threshold for glucose is between 0.16 per cent. and 0.17 per cent. of blood concentration.

As we have said, one of the main objects of our study was to gain information from this neglected field. For the purpose the blood and urine were examined at frequent intervals after the administration of glucose or the injection of epinephrin in the hope that we would in a number of instances hit on the point of blood sugar concentration where sugar just begins to appear in the urine, or to disappear from it. Table 35 shows the renal threshold in the instances in which it could be estimated with reasonable accuracy. The charts show the experiments in detail and full data are given in the tables accompanying the uncharted cases.

SUMMARY

In normal persons the renal threshold is not a constant factor, but is usually above 0.17 per cent. of blood sugar concentration, and in the few instances where it could be determined accurately it lay between 0.17 per cent. and 0.18 per cent. In two instances, and we have since found two more, the renal threshold was much lower, namely, below 0.14 per cent., and these persons may have glycosuria after carbohydrate feeding even though the blood sugar curve is within the normal reaction limits. The important practical significance of this observation need scarcely be emphasized. We predict that many otherwise healthy persons with occasional glycosuria will be found on careful observation to belong to this interesting group with low renal threshold. The relation of this group to renal diabetes is also obvious. No doubt further study will disclose persons with renal thresholds varying from the normal between 0.17 per cent. and 0.18 per cent. down to 0.08 per cent. and lower. At just what level will they be classed as renal diabetics? We think it altogether likely that no definite level can be fixed and that renal diabetes will remain, as it is, a relative condition. In this connection we wish to add the chart from a patient who clinically presents unusually well the characters of renal diabetes. The case has been reported in full by Lewis and Mosenthal,[17] After 100 gm. of glucose the blood sugar does not exceed 0.12 per cent., but a large amount of sugar is put out in the urine. Indeed, there is abundant glycosuria in the early morning when the fasting blood sugar is 0.84 per cent.

In nephritis the renal threshold is often above 0.20 per cent. That there is a high renal threshold in nephritis is generally known, but it is very puzzling to explain why some patients with nephritis have a high threshold and others, clinically identical, have a normal threshold. Case 18 in this series with marked hypertension and a phthalein output of 33 per cent. had a normal threshold. Recently we observed a patient with a blood pressure well over 200 mm. Hg, and a phthalein

17. Lewis and Mosenthal: Bull. Johns Hopkins Hosp., 1916, **27**, 133.

output of only 15 per cent. who had a low renal threshold for glucose, namely, in the neighborhood of 0.15 per cent.

The patients observed by us with disturbed thyroid function and various other conditions had a renal threshold between 0.17 per cent. and 0.18 per cent. Case 26 with exophthalmic goiter and evidence of a mild nephritis had a slightly higher threshold, namely, between 0.19 per cent. and 0.2 per cent.

In diabetes very interesting variations are discovered. In the mild cases the renal threshold is at the normal level, but in a number of the moderately severe cases and in one of the severe the threshold was below 0.15 per cent. Our studies were made on patients who had become sugar free after treatment, and in this series we were not fortunate enough to discover any with a high threshold. However, there is abundant clinical evidence to illustrate the frequency of a high threshold in this disease. In the terminal stages it is almost the rule, and it must be emphasized that the renal impermeability is by no means constantly associated with a nephritis that is demonstrable clinically. The renal threshold for glucose is an important practical factor in the study of diabetes. It will be interesting to discover the clinical differences between the patients with low and those with high thresholds and to determine under what conditions the threshold may vary, for it may vary in the same patient.

Finally, we wish to call attention to one more important feature of our studies. It will be noted that in many instances when there is a considerable glycosuria the excretion of sugar continues long after the blood sugar has fallen below the level at which it first appeared. Charts 3, 4, 14, 17 and 28 illustrate the condition very well.

CONCLUSIONS

1. In normal persons after 100 gm. of glucose there is only a moderate hyperglycemia that rapidly subsides, the blood sugar remaining below 0.15 per cent. and again reaching the fasting level or in many instances a still lower level in from one to two hours.

2. In patients with a lowered carbohydrate tolerance, notably in diabetes, the hyperglycemia is more pronounced and more prolonged, the blood sugar usually exceeding 0.2 per cent. and the reaction lasting from three to five hours.

3. Increased carbohydrate tolerance is indicated by a subnormal reaction, the blood sugar in such instances showing only an insignificant rise.

4. As far as may be judged from the alimentary test the disturbance of glucose utilization is essentially the same in diabetes and in other conditions with low sugar tolerance, such, for instance, as is commonly found in nephritis and in deranged thyroid and hypophysial function.

5. The renal threshold for glucose in normal persons is between 0.17 per cent. and 0.18 per cent. of blood concentration.

6. The normal threshold is likewise found in many patients with lowered carbohydrate tolerance.

7. Some otherwise normal persons have a low renal threshold, that is, below 0.14 per cent. This observation has an important bearing on our conception of renal diabetes.

8. Many cases of nephritis have a high threshold, so that although the blood sugar may exceed 0.2 per cent. only a trace of sugar or none appears in the urine.

9. Mild cases of diabetes usually have a normal threshold; many severe cases have a lowered threshold. This lowered threshold may be a factor in the severity.

10. As the kidneys excrete sugar there is a tendency for the threshold to fall so that although sugar may first appear when the blood sugar reaches 0.17 per cent., sugar may still be excreted after it has dropped to 0.1 per cent.

11. A study of alimentary hyperglycemia and glycosuria as carried out in these observations gives a valuable insight into the carbohydrate economy. The test is particularly valuable to investigate patients with slight or occasional glycosuria. It decides at once whether the glycosuria is due to a metabolic disturbance, to a low renal threshold or to a combination of both factors. If the renal threshold be high it may indicate a more serious disturbance of glucose utilization than the slight glycosuria would suggest.

12. Following the subcutaneous injection of epinephrin a marked hyperglycemia occurs that reaches its maximum in one hour and then subsides as rapidly as it arose, the whole reaction occupying two hours.

13. There is no relation between the degree of alimentary hyperglycemia and the degree of epinephrin hyperglycemia.

14. When the alimentary glucose test shows certain abnormalities in the character of the blood sugar reaction these same abnormalities are reproduced in the epinephrin curve.

15. The action of epinephrin on sugar metabolism is independent of its other actions; there is no constant relation between the hyperglycemia, the vascular effects and the diuresis.

16. Epinephrin has no effect on the renal permeability for glucose.

17. Atropin diminishes the effect of epinephrin on the mobilization of sugar; pilocarpin usually increases the effect. When atropin acts in this respect as a marked depressant, pilocarpin has little or no influence; when atropin acts but slightly, pilocarpin greatly exaggerates the epinephrin effect.

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OBSERVATIONS ON KIDNEY FUNCTION IN DIABETES MELLITUS *

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In the history of diabetes numerous theories as to the cause of the disease have been proposed, although no single one has had an anatomic basis definite enough to establish the underlying pathologic process. At present, while the etiology of diabetes is believed by most observers to be due to insufficiency of the internal secretion of the pancreas, yet pathologic anatomists have demonstrated that the kidneys of diabetic patients usually show certain well defined and characteristic lesions.

Armanni[1] was the first to point out that in diabetes there was an almost specific injury to the epithelium of the straight tubules by which they lost their cytoplasm and were transformed into hyaline-like vesicles without definite structure. Ebstein[2] confirmed this finding and described in coma a typical massing together of necrotic cells. Finally, Ehrlich[3] proved that the peculiar hyaline degeneration described by Armanni was due to the deposition of glycogen in the cells and that the so-called "glycogenic degeneration" could be found in the majority of cases.

Albertoni and Pisenti[4] fed rabbits and dogs with acetone, producing first albuminuria and eventually hyaline changes analogous to those already described, without, however, causing glycogenic degeneration. Trambusti and Nesti[5] were able to produce similar lesions in phlorizinized dogs when the animals excreted appreciable amounts of acetone in the urine. Thus it has been shown by both clinical and experimental material that the diabetic kidney has a more or less definite anatomic appearance which is comparable to that obtained in animals associated with the passage of acetone bodies from the blood into the urine. In view of these findings it is interesting that no systematic studies as to the relation of the kidney function to diabetes have been recorded. Work already reported and abundantly confirmed, however, has brought out four interesting features in this respect.

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1. Armanni: Quoted by Cantani, Le diabète sucré et son traitement dietetique, 1876.
2. Ebstein: Deutsch. Arch. f. klin. Med., 1881, **28,** 143; 1882, **31.**
3. Ehrlich: Ztschr. f. klin. Med., 1883, **6,** 33.
4. Albertoni and Pisenti: Arch. f. exper. Path. u. Pharmakol., 1887, **23,** 393.
5. Trambusti and Nesti: Ziegler's Beitr. z. path. Anat., 1893, **14,** 337.

First, the diabetic kidney is at times under the influence of a diuretic. This has been shown most simply by the characteristic symptoms of polyuria and polydipsia, and somewhat more systematically by the relation between the day and night urine. Laspeyres[6] found a nocturnal polyuria in two out of five cases of diabetes studied, and Carles[7] in six cases. Lépine mentions that in diabetes the normal difference between day and night urine is less marked, an observation confirmed by Péhu[9] and Külz.[10]

Secondly, albuminuria either constant, intermittent or terminal, is found in many cases. Thus Aldehoff[11] found albuminuria in 79 per cent. of 680 observations, von Noorden[12] in 21 per cent. of 650 observations, and various other writers in from 10 to 68 per cent. of their cases. While the discrepancy in figures is wide, possibly owing to the different methods of analysis employed, yet the fact remains that the diabetic kidney is abnormally prone to albuminuria.

Thirdly, edema may occur. Naunyn[13] says that edema is not a rare occurrence in cachetic patients with severe diabetes. Williamson[14] has observed anasarca in more than 5 per cent. of his patients, Frerichs[15] in twenty-five out of 400 cases, and Joslin and Goodall[16] in seven cases at a time when the patients presented slight, if any, other evidence of heart or kidney disease.

Finally, the urine of patients on the verge of coma has been found repeatedly to contain masses of hyaline and granular casts, the so-called "Komazylinder" of Aldehoff.

The present paper reports studies on renal function in diabetes under varying conditions of glycosuria, hyperglycemia and acidosis. It seemed of greatest interest to study the effect on the kidney of sugar and acetone bodies because they are usually not a feature in nephritis. Moreover, it is generally believed that an increasing concentration of sugar in the blood without concomitant glycosuria is due to a specific holding back of sugar on the part of the diabetic kidney, a fact which in itself is evidence of abnormal kidney function. Under normal conditions, too, the organism depends on the kidney to regulate the acid-base equilibrium. Unless the rate of elimination of acids keeps up

6. Laspeyres: Deutsch. Arch. f. klin. Med., 1900, **68,** 192.
7. Carles: Province méd., 1906.
8. Lépine: Le diabète sucré, 1909.
9. Péhu: Revue de méd., 1903, p. 279.
10. Külz: Klinische Erfahrungen über Diabetes mellitus, 1899.
11. Aldehoff: Quoted from Külz, Footnote 10.
12. Von Noorden: Die Zuckerkrankheit und ihre Behandlung, 1912.
13. Naunyn: Diabetes Mellitus, 1906.
14. Williamson: Diabetes Mellitus and Its Treatment, 1898, p. 227.
15. Frerichs: Ueber den Diabetes, 1884.
16. Joslin and Goodall: Experiments on an Ash-Free Diet and Salt Metabolism, Jour. Am. Med. Assn., 1908, **51,** 727.

with their rate of production, true "acidosis" results. Thus the permeability of the kidney for both sugar and acid may well be an important factor in helping to establish the symptoms due to glycosuria and acidosis.

At present, the common tests for renal function used in heart and kidney diseases in addition to urinalysis are the phenolsulphonephthalein test of Rowntree and Geraghty,[17] some form of "test renal meal" as advocated by von Monakow,[18] Hedinger and Schlayer,[19] O'Hare[20] and Mosenthal,[21] estimation of nonprotein nitrogen or urea of the blood alone as advocated by Ascoli,[22] Strauss,[23] and Folin,[24] or in relation to the simultaneous excretion of urea in the urine according to the method of Ambard[25] and McLean,[26] and estimation of the blood chlorid in relation to its excretion in the urine according to Ambard's laws. Comparative studies with those tests in nephritis have shown that as the renal function becomes impaired, the excretion of phenolsulphonephthalein diminishes, the nonprotein nitrogen and urea of the blood increase, the kidney is less able to excrete nitrogen and in certain instances water and sodium chlorid, and the ratio between urea in the blood and that in the urine changes so that Ambard's constant for urea becomes higher as McLean's index becomes proportionally lowered. Interesting information in regard to renal physiology has been obtained by such tests and two significant conclusions have been drawn: (1) Ambard and McLean have demonstrated that the excretion of certain substances from the blood through the kidney into the urine is carried on according to laws capable of numerical expression. (2) The kidney has selective and independent powers of excretion for several of the different urinary constituents.

For the studies reported here a series of cases of diabetes of differing severity was selected. Renal function in relation to the excretion of urea and sodium chlorid was tested by McLean's adaptation of the Ambard constant. These tests seemed sufficiently comprehensive

17. Rowntree and Geraghty: Jour. Pharm. and Exper. Therap., 1909, **1,** 579.
18. Von Monakow: Deutsch. Arch. f. klin. Med., 1911, **102,** 248.
19. Hedinger and Schlayer: Deutsch. Arch. f. klin. Med., 1914, **114,** 120.
20. O'Hare: A Study of Salt, Nitrogen and Water Excretion in Nephritis, THE ARCHIVES INT. MED., 1916, **17,** 711.
21. Mosenthal: Renal Function as Measured by the Elimination of Fluids, Salt and Nitrogen, and the Specific Gravity of the Urine, THE ARCHIVES INT. MED., 1915, **16,** 733.
22. Ascoli: Arch. f. d. ges. Physiol., 1901, **87,** 103.
23. Strauss: Die Chronische Nierentzündungen in ihrer Einwirkung auf die Blutflüssigkeit und deren Behandlung, 1902.
24. Folin and Denis: Jour. Biol. Chem., 1912, **11,** 527.
25. Ambard: Physiologie Normale et Pathologique des Reins, 1914.
26. McLean: Clinical Determination of Renal Function by an Index of Urea Excretion, Jour. Exper. Med., 1915, **22,** 212, 336; Jour. Am. Med. Assn., 1916, **66,** 415.

because McLean has shown that the urea index is a good indicator of total renal function, gives practically the same information as the phenolsulphonephthalein test, and is preferable to those tests which rely on blood analysis alone, since they can be interpreted only when the intake of the substance studied is known. The chlorid excretion was determined in addition, to study renal function in more than one way. "Test meal" studies were not made because the cases differed so widely in severity as to make a common diet for all impossible. The blood and urine sugar, as well as the carbon dioxid tension of the alveolar air,[27] were estimated to disclose any relation between abnormal renal function, as illustrated by ordinary tests, and glycosuria or abnormal amounts of sugar or acetone bodies in the blood. Obviously, the carbon dioxid tension of the alveolar air gave an indirect measure of the blood acetone bodies. Winterstein[28] and Hasselbalch,[29] however, have established that variations in the carbon dioxid content of the blood, and consequently of the alveolar air, are inverse to the production of nonvolatile acids. Observations to be published in another paper show that in diabetes the fall in the alveolar carbon dioxid which occurs in acidosis is more or less parallel to the increase of acetone bodies in the blood; thus the information so obtained was significant.

The tests were all made in the same fashion according to McLean's adaptation of Ambard's methods. The patients were taken for observation in the morning before breakfast to avoid the effect of feeding. One-half hour before the period began the subjects were given 150 or 200 c.c. of water and took no more fluid or food until the observation period was ended. At the beginning of the period the bladder was emptied. Thirty minutes later about 25 c.c. of blood was taken from an arm vein into a dry tube containing about 100 mg. of powdered potassium oxalate to prevent clotting. At the same time samples of alveolar air were obtained. At the end of 72 minutes[30] after the bladder was first emptied, the specimen of urine secreted during the 72-minute period was collected, carefully measured and used for analysis.

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27. The carbon dioxid tension of the alveolar air was determined in the Peter Bent Brigham Hospital cases. In the others it was calculated from the capacity of the blood plasma to combine with carbon dioxid (Van Slyke: Jour. Biol. Chem., 1917, **30,** 289), the volume per cent. of carbon dioxid bound by the plasma being multiplied by 0.69 in order to make the results numerically comparable to alveolar carbon dioxid tensions expressed in millimeters of mercury. The results from the two methods are usually alike, as has been shown by Van Slyke and by Frothingham and Walker (THE ARCHIVES INT. MED., 1916, **18,** 304), although in diabetes the alveolar air sometimes indicates acidosis when the blood alkali is really normal (Stillman, Van Slyke, Cullen and Fitz: Jour. Biol. Chem., 1917, **31,** 405).

28. Winterstein: Arch. f. d. ges. Physiol., 1911, **138,** 167.

29. Hasselbach: Biochem. Ztschr., 1912, **46,** 403.

30. In a few cases the length of time was one or two hours. In such instances the blood was drawn in the middle of the time selected.

A 72-minute period was ordinarily taken, since it is one-twentieth of 24 hours, and the calculation of the rate of excretion for 24 hours was made simple.

A portion of the blood was analyzed for urea by the method of Van Slyke and Cullen,[31] and for sugar by the Benedict-Lewis[32] method, except in a few cases when Bang's[33] micromethod was used. The remainder of the blood was centrifugalized and the plasma pipetted off. A portion of the plasma was analyzed for sodium chlorid by the McLean and Van Slyke[34] method, and for the combining power for carbon dioxid according to Van Slyke's[35] method. Alveolar air samples were collected according to the Plesch[36] method and were analyzed in a Haldane[37] gas analysis instrument. Since the blood or air was taken in about the middle of the period, it was assumed to represent the concentration in the blood for the substances whose simultaneous excretion in the urine was studied. The urine was analyzed for sugar by Benedict's[38] method or polarization in a few instances; for chlorids by a modified Volhard titration; and for urea and ammonia by Van Slyke and Cullen's method. The results are divided into two groups dealing with (1) the urea index, and (2) the relation of plasma chlorid to the excretion of chlorid in the urine.

In Table 1 are recorded observations on the urea index. In considering the results it is necessary to compare them with similar observations on normal individuals. McLean has published 107 such tests made according to the same methods, which serve as a good control. His tables show that the normal concentration of urea in the blood varies from 0.2 to 0.5 gm. per liter. The normal urea index varies between 80 and 200, with an average reading of 120 based on 100 tests. Any index below 80 is considered abnormal, and the degree of impairment of functional ability or damage to the kidneys becomes greater as the index gets lower. Any index above 200 is abnormal, although its significance is less certain. A high index may occur in healthy young individuals with low blood urea; it may result from the washing out of urea with a high fluid output; or it may occur with "vascular hypersensitiveness," according to the conception of Schlayer. Repeated indexes made on the same normal individual at different times may

31. Van Slyke and Cullen: Jour. Biol. Chem., 1914, **19,** 211.
32. Benedict and Lewis: Jour. Biol. Chem., 1915, **20,** 61.
33. Bang: Der Blutzucker, 1913.
34. McLean and Van Slyke: Jour. Biol. Chem., 1915, **21,** 361.
35. Van Slyke: Jour. Biol. Chem., 1917, **30,** 289.
36. Plesch: Ztschr. f. exper. Path. u. Therap., 1909, **3,** 380.
37. Haldane: Methods of Gas Analysis, 1912.
38. Benedict: The Detection and Estimation of Glucose in Urine, Jour. Am. Med. Assn., 1911, **57,** 1193.

TABLE 1.—The Relation of the Rate of Urea Excretion to Concentration in Blood Arranged According to the Urea Index

$$\text{Index (I)} = \frac{\text{Gm. per 24 hrs.} \sqrt{\text{Gm. per liter}} \times 8.96}{\text{Wt. in Kg.} \times (\text{Blood Urea})^2}$$

Number	Subject	Weight, Kg.	24 Hour Urine, C.c.	Urea			Index I
				Gm. per Liter of Blood Ur	Gm. per Liter of Urine C	Gm. per 24 Hrs. D	
1	P. B. B. H. 6353	30.0	3,600	0.726	6.99	25.20	37
2	P. B. B. H. 6493	70.6	3,072	0.458	9.09	27.92	50
3	R. I. H. 2341	54.0	1,694	0.167	3.72	6.30	72
4	Fl.	45.0	6,000	0.300	4.16	25.00	79
5	R. I. H. 2234	50.0	2,000	0.410	12.35	24.70	93
6	R. I. H. 2480	47.0	1,680	0.273	8.11	13.62	100
7	P. B. B. H. 5921	61.7	2,880	0.287	6.76	19.47	104
8	R. I. H. 2128	40.2	1,500	0.314	10.05	15.10	108
9	P. B. B. H. 5988	40.0	4,800	0.280	3.94	18.91	108
10	P. B. B. H. 6328	68.3	1,200	0.494	30.77	36.92	110
11	P. B. B. H. 5975	64.0	1,080	0.377	25.66	27.71	138
12	P. B. B. H. 6364	64.2	1,500	0.265	12.60	19.66	139
13	R. I. H. 2280	28.5	800	0.232	9.64	7.70	140
14	P. B. B. H. 6032	48.0	1,440	0.257	10.75	15.48	144
15	R. I. H. 2080	48.0	2,000	0.302	8.88	17.76	144
16	R. I. H. 2535	47.8	4,080	0.190	3.60	14.70	145
17	L. T.	50.0	2,540	0.260	8.00	20.58	156
18	R. I. H. 2111	49.2	5,400	0.225	4.07	22.00	160
19	R. I. H. 2684	31.7	6,740	0.169	1.81	12.20	162
20	P. B. B. H. 6483	61.9	1,200	0.272	17.61	21.13	174
21	C. R.	37.3	3,460	0.162	3.11	10.75	175
22	R. I. H. 2282	46.5	1,740	0.220	9.16	15.94	192
23	P. B. B. H. 6205	62.0	780	0.212	18.23	14.22	198
24	R. I. H. 2516	87.2	2,997	0.307	15.40	46.13	198
25	R. I. H. 2414	39.8	1,280	0.165	7.11	9.09	200
26	M. L.	64.0	3,840	0.218	6.98	26.80	205
27	R. I. H. 2394	42.0	2,800	0.215	6.37	17.70	206
28	P. B. B. H. 5564	52.0	3,360	0.135	3.51	11.79	210
29	Fl.	95.4	6,000	0.230	7.44	44.64	217
30	Dl.	48.7	2,200	0.192	7.38	16.24	220
31	R. I. H. 2487	50.2	1,800	0.092	3.26	5.86	223
32	R. I. H. 2469	50.4	5,000	0.160	4.17	20.85	296
33	C. A.	60.0	2,000	0.222	10.60	30.74	305
34	R. I. H. 2686	25.8	2,700	0.169	2.52	6.80	315
35	P. B. B. H. 5393	65.6	1,500	0.210	16.71	25.06	320
36	R. I. H. 2457	52.2	3,500	0.132	7.62	26.67	550
37	R. I. H. 2679	41.2	3,400	0.115	5.06	17.20	635
38*	P. B. B. H. 6482	71.3	7,220	0.240	20.65	151.16	1498

* Excluded from table of averages.

show such marked differences as from 87 to 196. The meaning of such variation is not defined.

Table 1 shows that twenty-one cases of diabetes, or 56 per cent. of those studied, have a urea index within normal limits. Thirteen cases, or 34 per cent., have an index above 200; four cases, or 10 per cent., have an index below 80, and must therefore be considered to have an impaired renal function. It is of interest that such a large number of cases should have a high index, especially when it is realized that the average index of those cases within normal limits is 146, which is significantly higher than McLean's normal average of 120. One reason for such findings may be the low blood urea found in several cases. Thus Case 31, with an index of 223, had a blood urea of 0.092 gm. per liter, Case 25 an index of 200, with 0.165 gm. of urea per liter of blood, and Case 28 an index of 210, with 0.135 gm. of urea per liter of blood. A more probable explanation lies in the high fluid output which occurred frequently. For instance, in the thirteen cases with an index above 200, the rate of water excretion for twenty-four hours was never below 1,500 c.c., in one case it reached 7,320 c.c., and averaged 3,770 c.c., while in the entire series the lowest output was 780 c.c. per twenty-four hours, and the average was 3,034 c.c. In McLean's normals, on the other hand, the highest fluid output encountered was 5,400 c.c., the lowest was 462 c.c., while the average was 1,738 c.c.

The patients, both normal and diabetic, had taken the same amount of fluid to drink at the same time before the period was begun. It therefore seemed that the diabetic kidney often had a rate of water elimination more rapid than normal. Since acids or sugar might possibly produce such a diuretic effect, the rate of water excretion per twenty-four hours was compared with the height of blood sugar, with the glycosuria, and with the degree of acidosis in those cases with a normal or high urea index. The results of this study are shown in Table 2.

The results studied from this point of view are inconclusive. Of the thirty-four observations, twenty-three had a fluid output above the average normal rate of 1,740 c.c. in twenty-four hours. In this group acidosis could not be assumed to produce the polyuria, as cases with a low alveolar air showed no tendency to excrete more fluid than did those with high alveolar air. Twelve cases showed an appreciable excretion of sugar. The fluid output in these cases bore relation neither to the total excretion in twenty-four hours nor to the concentration of sugar per liter of urine. The sugar-free cases appeared to excrete water with as much ease as those with glycosuria. It is of possible significance that only four of the twenty-three cases had a blood sugar below 0.17 per cent. This observation alone might suggest that hyper-

TABLE 2.—The Relation of the Rate of Water Excretion in Twenty-Four Hours to Sugar Excretion, and to Concentration in the Blood of Sugar or Acids (as Estimated by the Carbon Dioxid Tension of the Alveolar Air) in Those Cases of Diabetes with a Urea Index Above 80. Tabulated According to the Fluid Output

Number	Subject	Weight, Kg.	24-Hour Urine, C.c.	Sugar			Alveolar CO_2, Mm.
				Gm. per Liter of Blood S	Gm. per Liter of Urine C	Gm. per 24 Hrs. D	
1	P. B. B. H. 6482	71.3	7,320	3.40	18.50	135.42	39.9
2	R. I. H. 2684	31.7	6,740	1.37	Negative	.....	42.6
3	Fl.	95.4	6,000	2.26	7.50	45.00	35.0
4	R. I. H. 2111	49.2	5,400	2.00	Traces	.....	37.8
5	R. I. H. 2469	50.4	5,000	1.33	Negative	.....	38.9
6	P. B. B. H. 5938	40.0	4,800	3.18	12.50	60.00	12.8
7	R. I. H. 2525	47.8	4,080	1.56	Negative	.....	40.2
8	P. B. B. H.	64.0	3,840	1.49	Negative	.....	40.8
9	R. I. H. 2457	52.2	3,500	2.94	18.52	64.82	23.2
10	C. B.	37.3	3,469	2.62	32.30	111.50	15.5
11	R. I. H. 2079	41.2	3,400	2.86	Negative	.....	43.2
12	P. B. B. H. 5564	52.0	3,360	2.20	Negative	.....	37.3
13	R. I. H. 2516	57.2	2,997	2.63	16.40	49.14	28.8
14	P. B. B. H. 5921	61.7	2,880	2.16	Traces	.....	31.6
15	R. I. H. 2294	42.0	2,800	2.33	22.20	62.00	20.2
16	C. A.	60.0	2,900	2.50	23.80	69.02	35.0
17	R. I. H. 2686	25.8	2,700	2.00	Negative	.....	41.3
18	L. T.	50.0	2,540	2.56	41.60	106.00	29.6
19	Dl.	48.7	2,200	4.35	34.48	75.85	36.8
20	R. I. H. 2030	48.0	2,000	3.00	16.00	32.00	20.1
21	R. I. H. 2234	50.0	2,000	2.08	Negative	.....	38.2
22	R. I. H. 2487	50.2	1,800	2.38	Negative	.....	42.2
23	R. I. H. 2382	46.5	1,740	3.12	22.30	40.37	35.3
24	R. I. H. 2480	47.0	1,680	4.16	Traces	.....	33.0
25	P. B. B. H. 6364	64.2	1,500	1.37	Negative	.....	38.2
26	P. B. B. H. 5593	65.6	1,500	1.72	Negative	.....	42.5
27	R. I. H. 2123	40.2	1,500	2.08	Negative	.....	26.2
28	P. B. B. H. 6022	48.0	1,440	1.03	Negative	.....	39.1
29	R. I. H. 2414	39.8	1,280	1.67	Negative	.....	47.6
30	P. B. B. H. 6483	61.9	1,200	2.92	31.00	37.20	33.9
31	P. B. B. H. 6328	68.3	1,200	2.56	22.00	26.40	35.1
32	P. B. B. H. 5975	64.0	1,080	1.43	Negative	.....	38.7
33	R. I. H. 2280	28.5	800	3.12	Negative	.....	36.9
34	P. B. B. H. 6005	62.0	780	2.82	Negative	.....	32.5

glycemia was an important factor in diuresis. But against this are the eleven cases with a more nearly normal fluid output, five of which had a hyperglycemia well above 0.17 per cent.

On the whole, it appears from this series of cases that many diabetics have an abnormally high urea index. This is probably due in part to a washing out of urea through an increased output of fluid. Such polyuria does not depend on acidosis or glycosuria, but is apt to be coincident with a pronounced hyperglycemia. These findings suggest that the diabetic kidney is ordinarily hyperfunctional and hypersensitive to such a diuretic as an increased amount of sugar in the blood. They may explain in a measure the observations of earlier workers who commented on the frequency of nocturnal polyuria in the disease.

Of much greater interest both from the point of view of kidney function and diabetes are those cases with a urea index below 80, or, in other words, those cases with a definitely impaired renal function. These cases will be discussed in detail and will include certain other cases which should be placed in the same group for comparison. The cases fall into two divisions, the first consisting of one case in which the abnormal renal function was probably due to a coexistent chronic nephritis, and the second including seven cases of impending or true diabetic coma.

REPORT OF CASES

The first case, R. I. H. 2341, was a Russian woman aged 51. During a pregnancy twenty-eight years previously, the patient apparently had an attack of acute nephritis which recurred a year before entry to the hospital. Her diabetic symptoms were of two and one-half years' duration. Her physical examination was essentially negative except for an enlarged heart with an apical systolic murmur, and a blood pressure which on repeated examinations was above 190 systolic. The urine had a large trace of albumin and was without casts in the sediment. In view of the patient's history and physical examination it seemed probable that the urea index of 72 was due to a chronic nephritis, and was independent of her diabetes, which was relatively mild.

Of the coma cases, the first, C. R., was a young woman 30 years old. Her diabetes was of three years' duration, had shown a progressive, downward tendency and was accompanied by great emaciation and weakness. When seen, her physical examination was negative. Mentally she was bright, and said that she was no more uncomfortable than she had been for a year. Her breathing, however, was abnormally deep, and her pulse was small and rapid. The carbon dioxid tension of her alveolar air was 15.5 mm. The urine contained acetone, diacetic acid and much sugar. There was a large trace of albumin and the sediment contained many hyaline and granular casts. Renal function tests showed a urea index of 280. The patient was treated by her own physician who reported her death about ten days later.

Three cases were seen at shorter intervals before death.

Fl. was a Russian aged 60 years, with diabetes of several years' duration. A month previously he developed a carbuncle on his neck, which was still draining, though apparently in good condition. Two days before being seen he became alarmingly sleepy and short of breath. When seen, he still could be

roused, though he was evidently in a serious condition. His physical examination was negative except for his carbuncle and a diffuse bronchitis. His pulse was rapid and weak. His breathing showed marked air hunger. The urine contained much acetone, diacetic acid and sugar, had a heavy trace of albumin, and was loaded with hyaline and granular casts. Here again the carbon dioxid tension of the alveolar air was low (23.2 mm.). The urea index was 79. The patient continued to grow worse and died in a few days. No further studies on renal function could be made.

The third case, P. B. B. H. 6353, was that of a boy aged 13 years, with symptoms of diabetes of a few months' duration. The day before entry he suddenly became dyspneic and went into deep coma. His urine in addition to acetone, diacetic acid and sugar, contained a large trace of albumin and had showers of hyaline and granular casts in the sediment. The renal function tests showed a urea index of 36.5, pointing to a severe injury to his kidneys. Associated with this was a carbon dioxid tension in the alveolar air of 12.8 mm. The patient died in a few hours.

The fourth case, R. I. H. 2787, was a girl aged 12 years. Her diabetes was of a year's duration. She first entered the hospital Nov. 16, 1916, with considerable acidosis and glycosuria which cleared up under treatment. At the time of entry her urine contained albumin and casts, her urea index was 510, her glycosuria was 27 gm. to the liter or 89 gm. in twenty-four hours, and her blood sugar was 0.31 per cent. Her alveolar carbon dioxid tension was 23.3 mm. She was discharged Dec. 23, 1916, in good condition.

She reentered March 10, 1917, in coma. According to the history she had been well until the day before, when she began to feel "short of breath" and subsequently had grown stuporous. She died in a few hours after reaching the hospital. Her urine on this admission contained more albumin than on the time before, but fewer casts. Her urea index was 34, her glycosuria was 9.52 gm. to the liter or 33.74 gm. in twenty-four hours, and her blood sugar was 0.46 per cent. Her alveolar carbon dioxid tension was 10 mm.

If these four cases are grouped together as one, it is seen that as coma developed the renal function grew worse. This was best shown by the rapidly falling urea index. It so happened, moreover, that in each case the concentration and total output of sugar were comparable, yet the blood sugar increased as the urea index fell, an observation suggesting that the kidney was becoming impermeable to sugar as well as urea.

Opportunity to inquire more specifically into kidney function in diabetic coma was afforded by three other cases which were studied for several successive days.

P. B. B. H. 6493, was a woman aged 60 years. Her history was unimportant except for a characteristic diabetic history of ten years' duration. Until a week before entry into the hospital she had been reasonably comfortable. Then for no apparent reason she had become worse and on the day of entry was nearly comatose.

She was a very plethoric, obese woman. Her physical examination was negative except as to urine and blood analyses. She lived five days. By way of treatment she was fasted and was given fluids, soup, whisky and sodium bicarbonate in large doses. The progress of her illness and its effect on renal function is shown in Table 3.

At entry the urine contained albumin and casts in addition to sugar, acetone and diacetic acid. It was evident from these signs, as well as on account of such a low carbon dioxid tension of the alveolar air (23.7 mm. tension) that she had a marked acidosis. Clinically, during the three days following admis-

sion she appeared to improve. Her kidney function, however, grew worse despite the fact that enough alkali must have been absorbed to neutralize her acidosis in part and to cause a definite rise in the carbon dioxid tension of her alveolar air. On the morning of the fifth day the urea index was only 6. Her condition was so bad that it was impossible to obtain a specimen of alveolar air for analysis. She died within a few hours.

TABLE 3.—CASE P. B. B. H., 6493

Date	Wt., Kg.	24 Hr. Urine	Urea			Index	Sugar			Alveolar CO_2, Mm.
			Gm. per Liter Blood Ur	Gm. per Liter Urine C	Gm. per 24 Hrs. D		Gm. per Liter Urine C	Gm. per 24 Hrs. D	Gm. per Liter Blood B	
8/29/15	70.6	3,072	0.458	9.00	27.92	50	51.5	158.2	5.65	23.7
8/30/15	71.5	2,990	0.458	7.88	23.32	30	17.0	50.3	5.60	17.1
8/31/15	71.5	3,840	0.304	4.22	16.21	45	9.20	35.0	5.60	24.7
9/ 1/15	69.8	2,880	0.314	3.97	11.43	20	7.00	20.0	4.55	38.6
9/ 2/15	69.8	2,240	0.406	2.74	6.22	6	10.00	22.4	6.80	Not obtained

The excretion of sugar in this case is noteworthy. At entry the blood sugar was high and was accompanied by a relatively high sugar output. Under fasting the blood sugar showed a slight diminution, with a sudden rise taking place just before death. The sugar excretion on the other hand showed a persistent decrease.

P. B. B. H. 5938 is a similar case. The patient was a young woman aged 30 with an unimportant history except for diabetes. This was of two years' duration and had caused marked loss of weight and emaciation. The day before entry to the hospital she had become dyspneic and stupid. At entry she could still be roused but had pronounced air hunger. Her physical examination was negative except for her blood and urine. She died three days after

TABLE 4.—CASE P. B. B. H., 5938

Date	Wt., Kg.	24 Hr. Urine	Urea			Index	Sugar			Alveolar CO_2, Mm.
			Gm. per Liter Blood Ur	Gm. per Liter Urine C	Gm. per 24 Hrs. D		Gm. per Liter Urine C	Gm. per 24 Hrs. D	Gm. per Liter Blood S	
6/30/15	40.0	4,800	0.280	3.94	18.91	108	12.50	60.00	3.18	17.9
7/ 1/15	40.0	4,380	0.355	4.00	17.52	62	13.00	57.00	3.72	19.5
7/ 2/15	40.0	4,016	0.374	2.50	10.00	25	23.00	92.00	5.35	12.8

entry. Her treatment in the hospital consisted in whisky and fluids by mouth. In addition she was given infusions of sodium bicarbonate and glucose. Tests for renal function gave results shown in Table 4.

In this case, as well, the urea index showed a rapidly progressing drop, which may have been hastened by the fact that the acidosis was not appreciably influenced by the alkali. The blood sugar rose but interpretation of the findings in respect to it are obscured because the patient had received glucose.

R. I. H. No. 2770, was a boy aged 9 years. His diabetes was of two years' duration. On Oct. 28, 1916, he was in fairly good condition though the urine showed some sugar and a moderate ferric chlorid reaction. He entered the hospital two days later on the verge of coma. He lived for eight days, during which time he was practically comatose. At first he was fasted and given sodium bicarbonate by mouth. On the seventh day he was given two eggs and 5 gm. of carbohydrate in vegetables. Tests for renal function are given in Table 5.

TABLE 5.—TESTS FOR—

Date	Weight, Kg.	Urine per 24 Hrs., C.c.	Urea			Index	Sugar		
			Gm. per Liter of Blood Ur	Gm. per Liter of Urine C	Gm. per 24 Hrs. D	I	Gm. per Liter of Blood S	Gm. per Liter of Urine C	Gm. per 24 Hrs. D
10/31/16	14.6	535	0.332	4.20	2.25	26.0	4.55	4.00	2.14
11/ 1/16	14.4	1,200	0.763	2.79	3.35	4.3	2.64	1.85	2.22
11/ 2/16	14.0	1,200	1.61	5.13	6.16	3.3	4.20	4.55	5.47
11/ 3/16	13.8	1,000	0.715	5.00	5.00	14.4	4.11	5.89	5.89
11/ 4/16	13.5	1,500	0.620	4.61	7.91	29.0	5.56	6.25	9.39
11/ 6/16	13.1	1,400	0.497	3.22	4.50	29.0	5.56	3.65	5.11
11/ 7/16	12.7	800	0.730	4.34	3.46	9.6	5.00	9.09	7.26

* Acetone bodies in blood and urine determined by Van Slyke's method.

In this case the urea index fell at first from 26 to 3 and then rose slightly. On the day before death it fell again. The blood sugar remained high with a comparatively small excretion of sugar in the urine. The alveolar carbon dioxid tension was low at first but rose, probably as the result of sodium bicarbonate. When the sodium bicarbonate was omitted it fell again, but returned toward normal with food. The day before death it was 33.4 mm., which would justify the conclusion that acidosis alone was not sufficient to be fatal.

Unfortunately acetone determinations were not made in the other cases. In this, however, the findings are noteworthy. The blood acetone rose to tremendously high figures while sodium bicarbonate was being given, and diminished in the blood when the drug was omitted and food was taken. On the other hand, the urinary excretion of acetone in no way kept pace with the blood concentration.

It is interesting to contrast these results with two severe cases which improved immediately under treatment and on which repeated tests were made.

R. I. H. 2680 was a woman aged 28 years with a history of diabetes developing four months before entry to the hospital. A week before, she had noticed increasing polyuria and polydipsia accompanied by dyspnea on slight exertion. Her physical examination was negative except for slight air hunger. Her urine at entry contained a trace of albumin, without casts in the sediment. There was much sugar, and a heavy diacetic acid reaction. While under observation she was fasted until she became sugar-free and was then given a diet sufficiently low in protein carbohydrate and fat to keep her urine free from sugar.

R. I. H. 2475 was a boy aged 26 months. He had been a healthy child until three weeks before entry. Then there had been a gradual onset of polyuria, polydipsia, and polyphagia. At entry the child was drowsy and extremely irritable. His physical examination was essentially negative. He was treated by fasting, after feeding for one day, and was then given carbohydrates in green vegetables to his point of tolerance. The renal function tests on the two cases are grouped together.

—Renal Function

Acetone Bodies (including Beta-hydroxybutyric Acid)*			Alveolar CO_2, Mm.	Urinary Findings	Remarks
Mg. per 100 C.c. of Blood A	Gm. per Liter of Urine C	Gm. per per 24 Hrs. D			
150.0	8.00	4.26	15.8	Albumin and casts	250 sodium bicarbonate
240.0	7.91	9.50	20.2	Albumin and casts	60 sodium bicarbonate
260.0	7.76	9.32	30.3	Albumin and casts	150 sodium bicarbonate
270.0	7.20	7.20	34.7	Albumin and casts	20 sodium bicarbonate
368.0	4.54	6.80	26.8	Albumin and casts	
212.0	2.84	5.35	28.9	Albumin and casts	Fast broken
192.0	2.18	1.74	33.4	Albumin and casts	Fast broken

In both cases the urea index showed considerable variation from day to day without any progressive downward tendency. Other non-fatal cases which have been followed in similar fashion have shown variation in the urea index which, however, has usually remained well above normal. Occasional cases have been encountered which have shown temporary impairment of function. Some of these have been complicated by edema and one will be described in detail later.

These cases as a whole demonstrate two significant facts: Judged by the urea index, kidney function in diabetes is usually normal. In diabetic coma, on the other hand, pronounced renal insufficiency occurs. This is shown by a falling index which tends to become progressively lower as the severity of the condition increases. Such functional derangement may be accompanied by an increase in the blood sugar, with a lessened output, suggesting that other functions beside that of urea excretion are involved. At present the underlying cause of this complication is uncertain.

McLean has confirmed Ambard and Weill as to the laws of chlorid excretion in relation to its blood concentration and has tabulated seventy-two observations on normal individuals made according to the methods used in the present paper. McLean has found that normally the plasma chlorid varies between 5.62 and 6.25 gm. per liter according to the amount of salt ingested. There is a close agreement between

the chlorid calculated in the plasma by Ambard and Weill's constants and that actually found. The maximum differences in normal individuals were, with one exception, between 0.22 above the calculated value and 0.16 below. In one case the actual chlorid was 0.38 lower than the theoretical. Under pathologic conditions relatively increased concentration of chlorid occurs in certain types of cardiac and renal disease and usually accompanies edema. Relatively low concentration of chlorid occurs in fevers and under the influence of diuretics. There is no connection between urea and chlorid functions.

As can be seen from the table, in the twenty-eight cases of this series which were studied, the plasma chlorid varied between 5.05 and 6.31 gm. per liter. In eight cases the actual plasma chlorid was higher

TABLE 6.—Case R. I. H., 2680

Date	Weight, Kg.	24 Hr. Urine	Urea, Gm. per Liter Blood Ur	Index of Excretion I	Sugar			Alveolar CO_2, Mm.
					Gm. per Liter Blood S	Gm. per Liter Urine C	Gm. per 24 Hrs. D	
10/16/15	48.0	2,000	0.262	144	3.00	16.00	32.00	20.1
10/17/15	48.4	2,000	0.190	230	2.70	14.30	28.60	28.7
10/18/15	49.5	6,800	0.150	142	2.62	3.00	20.40	41.4
10/20/15	49.4	2,680	0.162	210	2.33	3.77	10.10	39.5
11/3/15	11.8	1,020	0.336	414	5.70	43.48	44.35	21.8
11/4/15	11.8	1,680	0.408	256	4.65	32.26	54.20	23.6
11/5/15	11.7	600	0.186	227	2.00	3.70	2.22	27.8
11/6/15	12.2	2,300	0.228	310	1.44	Traces	Traces	23.6
11/8/15	12.2	800	0.202	220	1.54	Negative	Negative	29.4

than the calculated, while in the remaining twenty it was lower. This confirms McLean, who found a similar lowering of the plasma chlorid in the majority of his observations on twenty-eight other cases of diabetes. By comparing the rate of chlorid excretion with the degree of acidosis, the urea index and the blood sugar, no interrelationship could be found. It would seem that in diabetes as well as nephritis the modes of excretion of urea and chlorid are independent.

Studies were made in three cases which may throw light on edema in diabetes.

R. I. H. 2394, was a man aged 31 years. He entered the hospital in March, 1915, with diabetes of short duration. His glycosuria responded to fasting and he was discharged sugar-free on a fairly liberal mixed diet. During his first stay in the hospital his urine was albumin-free and did not contain casts. For six months after discharge he did well. Then he grew careless, ate a

TABLE 7.—The Relation of the Rate of Chlorid Excretion (Calculated as Sodium Chlorid) to Concentration in Plasma, Arranged According to Rate of Excretion as Modified by Concentration in Urine and Expressed as

$$\text{Calculated plasma NaCl} = 5.62 + \sqrt{\frac{\text{Gm. per 24 hrs.} \quad \sqrt{\text{Gm. per liter}}}{\text{Wt. in Kg.} \times 4.23}}$$

Number	Subject	Weight, Kg.	24 Hrs. Urine, C.c.	Blood Urea per Liter	Index of Urea Excretion I	Blood Sugar per Liter	Alveolar CO_2, Mm.	Sodium Chlorid				
								Gm. per Liter of Urine C	Gm. per 24 Hrs. D	Gm. per Liter of Plasma		
										Calculated	Actual	Difference
1	P. B. B. H. 5038	40.0	4,800	0.280	108	3.18	17.9	0.20	0.96	5.67	5.56	−0.11
2	P. B. B. H. 6403	70.6	3,072	0.458	50	5.65	23.7	0 60	1.85	5 69	5.05	−0.64
3	P. B. B. H. 5593	65.6	1,500	0.210	320	1.72	42.5	1.70	2.55	5.78	6.35	+0.52
4	P. B. B. H. 6353	30.0	3,600	0.736	36	4.35	12.8	0.60	2.15	5.73	6.25	+0.52
5	R. I. H. 2680	48.0	2,000	0.262	144	3.00	20.1	1.70	3.40	5.77	6.01	+0 24
6	P. B. B. H. 5021	61.7	2,880	0.267	104	2.16	31.6	2.20	6.34	5.81	6.22	+0.41
7	P. B. B. H. 5975	64.0	1,080	0.377	138	1.43	38.7	5.10	5.51	5.83	6.31	+0.48
8	P. B. B. H. 6205	62.4	1,440	0.212	242	2.08	41.9	4.70	6.77	5.86	5.60	−0.26
9	R. I. H. 2341	54.0	1,694	0.167	72	1.25	41.0	4.40	7.45	5.88	5.87	−0.01
10	P. B. B. H. 6364	64.2	1,560	0.265	139	1.37	38.2	5.10	7.96	5.88	5.87	−0.01
11	P. B. B. H. 5564	52.3	3,360	0.135	210	2.30	37.3	2.70	9.07	5.88	6.02	+0.14
12	R. I. H. 2394	42.0	2,800	0.215	206	2.33	20.2	2.75	7.70	5.89	5.67	−0.22
13	R. I. H. 2457	52.2	3,500	0.152	550	2.14	23.2	2.90	10.15	5.90	5.26	−0.64
14	R. I. H. 2414	39.8	1,280	0.165	200	1.67	47.6	5.10	6.52	5.92	5.53	−0.39
15	C. A.	60.0	2,900	0.222	305	2.50	35.0	4.20	12.18	5.93	5.31	−0 62
16	Gl.	70.0	2,240	.....	84	1.10	38.1	5 50	12.32	5.93	6.03	+0.10
17	R. I. H. 2686	25.8	2,700	0.109	315	2.60	41.3	2.80	7.55	5.96	5.76	−0.20
18	R. I. H. 2234	50.0	2,000	0.410	93	2.08	38.2	5.78	11.56	5.98	5.33	−0.65
19	L. T.	50.0	2,540	0.260	156	2.56	29.6	5.60	14.20	6.02	5.26	−0.70
20	R. I. H. 2516	87.2	2,997	0.307	198	2.63	38.8	7.80	23.37	6.04	6.09	+0.05
21	Dl.	48.7	2,200	0.192	220	4.35	36.8	6.80	14.96	6.05	5.32	−0.73
22	R. I. H. 2684	31.7	6,740	0.169	162	1.37	42.6	2.45	16.50	6.06	5.45	−0.61
23	Ml.	64.0	3,840	0.218	205	1.49	40.8	5.90	22.66	6.07	5.89	−0.28
24	R. I. H. 2382	46.5	1,740	0.220	192	3.12	35.3	8.30	14.44	6.08	5.46	−0.62
25	R. I. H. 2111	49.2	5,400	0.225	160	2.00	37.8	4.30	23.20	6.10	5.88	−0.22
26	R. I. H. 2679	41.2	3,400	0.115	635	2.86	43.2	5.60	19.03	6.13	5.29	−0.84
27	P. B. B. H. 6032	48.0	1,440	0.257	144	1.03	39.1	12.80	18.43	6.19	5.31	−0.88
28	R. I. H. 2409	50.4	5,000	0.160	296	1.33	38.9	6.30	31.50	6.23	5.54	−0.69

diet beyond his tolerance, so that he showed sugar constantly and was on the decline. He reentered the hospital June 9, 1916, in poor condition. His physical examination was negative. His urine contained sugar and diacetic acid. There was a trace of albumin but no casts. The carbon dioxid tension of his alveolar air was 21 mm. His blood was strikingly lipemic. He was fasted for nine days with benefit to his acidosis and lipemia, although his glycosuria persisted. It seemed wise to interrupt his fast for four days by allowing a protein-fat diet of 1,000 calories. During this period he developed a tremendous edema so that he looked like a case of chronic nephritis. His color grew pasty, there was edema of his eyelids and genitals, as well as of his entire body.

A second fast for three days cleared his glycosuria. He was then given carbohydrates in the form of green vegetables to the point of tolerance, and finally a mixed diet of 1,700 calories containing 85 gm. of protein and 15 gm. of carbohydrate. He was discharged on this diet, sugar-free and acid-free. Repeated renal function studies were made up to and during the edema formation. They are shown in Table 8.

TABLE 8.—

Date	Weight, Kg.	Diet	Chlorid Intake	24 Hr. Urine	Blood Urea	Urea Index	Sugar		
							Gm. per Liter C	Gm. per 24 Hrs. D	Blood Sugar S
6/10/16	42.0	Mixed observation diet	10.00	2,800	0.215	205	22.20	62.00	2.33
6/12/16	42.0	Fasting	10.00	2,400	0.204	91	6.20	14.90	2.63
6/13/16	42.0	Fasting	10.00	1,600	0.195	78	9.40	15.09	2.56
6/14/16	42.0	Fasting	10.00	1,900	0.180	71	6.90	13.10	3.85
6/16/16	41.6	Fasting	10.00	1,600	0.215	83	12.50	20.00	3.23
6/26/16	50.0	Fasting	10.00	4,000	0.170	62	*	*	2.32
10/ 4/16	47.8	Mixed diet	—	4,900	0.302	210	Negative	Negative	1.22

* Heavy reaction not quantitated.

At the first observation the urea index was high and the patient was excreting chlorid with a plasma chlorid lower than the theoretical. As soon as fasting began the renal function became abnormal. This was shown by a falling urea index, a rising blood sugar with a lowering output, and by a marked chlorid retention and edema. Acidosis as estimated by both the alveolar carbon dioxid and actual amount of acetone in the blood diminished. It was only after the chlorid intake was restricted that the condition improved. Finally normal function returned. The effect of withdrawal of salt on the edema is shown graphically by the accompanying chart.

Two possible explanations of the condition come to mind. One is that the acetone bodies exert a specific effect on the kidneys. In support of this, there was presumably a considerable accumulation of acetone bodies in the tissues when the edema was at its height. Although the plasma bicarbonate was normal, the plasma acetone increased, which, according to Marriott[39] and Sassa,[40] shows that the

39. Marriott: Jour. Biol. Chem., 1914, **18**, 507.
40. Sassa: Biochem. Ztschr., 1914, **59**, 362.

acetone content of the organs was increased as well. Another explanation is that the patient had a true nephritis which cleared up under treatment. In either event the case illustrates the importance of following the chlorid balance in cases with edema.

Another factor of importance in the development of edema in diabetes is the manner in which the body reacts to sodium bicarbonate. It has been recognized that healthy individuals as well as diabetics will develop edema after they have taken continued large doses of the drug. Widal, Lemierre and Cotoni[41] followed the output of sodium chlorid in a patient who was given a known diet, and at the same time the body weight, the development of edema, and its connection with the intake

—Case R. I. H., 2394

Chlorid					Alveolar CO_2, Mm	Total Blood Acetone Bodies† (Gm. Acetone per Liter)	Urinary Findings
Gm. per Liter C	Gm. per 24 Hrs. D	Plasma Chlorid Cl	Calculated Plasma Chlorid	Difference			
2.75	7.70	5.67	5.89	—0.21	20.2	0.842	Albumin trace; no casts
1.74	4.17	5.40	5.80	—0.40	23.0	0.842	Albumin trace; few casts
1.35	2.16	5.25	5.74	—0.39	26.3	0.854	Albumin trace; few casts
1.15	2.18	5.48	5.73	—0.25	30.8	0.627	Albumin trace; no casts
1.30	2.08	5.27	5.73	—0.46	36.2	0.590	Albumin trace; no casts
0.50	2.00	5.58	5.70	—0.12	43.9	0.270	Albumin negative; no casts
—	—	6.23	—	.....	45.6	0.000	Albumin negative; no casts

† Blood acetone bodies determinations were made on plasma by Marriott's nephelometric method.

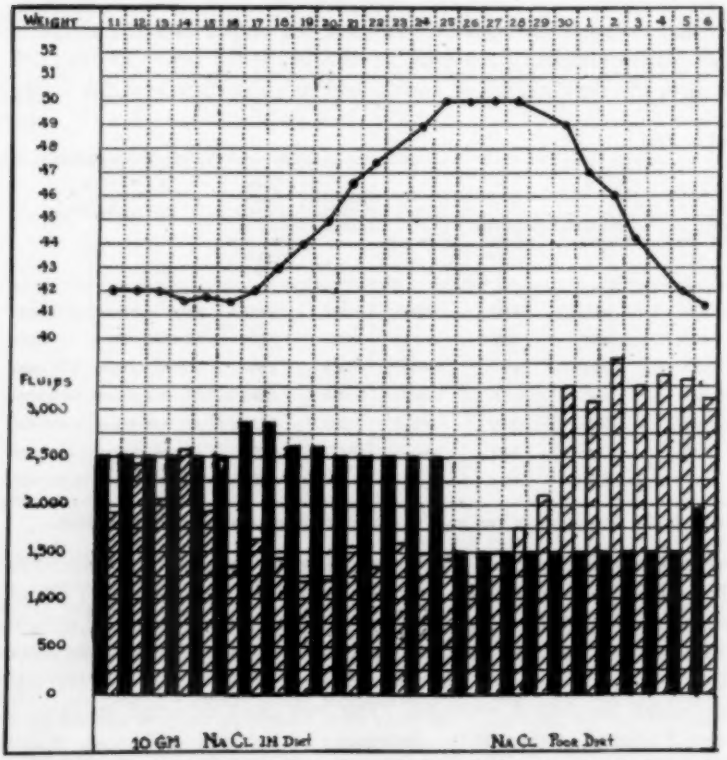
of sodium bicarbonate. They were able to demonstrate that when bicarbonate was given, the excretion of chlorid decreased and edema occurred. When the bicarbonate was discontinued, an excess of chlorid was excreted and the edema disappeared. From this they concluded that bicarbonate edema was not different from other edemas and depended on chlorid retention. The two cases reported in Table 9 would tend to confirm these observers.

In each case the plasma chlorid was lowered after the ingestion of an alkali, and, coincidentally, the rate of chlorid excretion in the urine. Since normal chlorid excretion bears a definite relationship to the plasma chlorid content, any agent lowering the latter would tend to suppress the output of the former. If large amounts of sodium chlorid were taken, and were not excreted on account of a plasma chlorid lowered by alkali, edema would naturally result.

41. Widal, Lemierre and Cotoni: Semaine méd., 1911, **31**, 325.

SUMMARY

Observations on renal function were made in a series of cases of diabetes mellitus. Urea excretion was studied by the urea index of McLean. Chlorid excretion in relation to its concentration in the blood plasma was studied by Ambard and Weill's constants. In addition, observations were made on the effect on renal function of varying degrees of acidosis, hyperglycemia and glycosuria.



Graphic representation of the effect of the withdrawal of salt from the diet on the edema in Case R. I. H. 2394.

The urea index in the majority of cases tended to be normal or abnormally high. This was in part due to the rapid rate of water elimination which characterized many of the cases. Such diuretic effect was not dependent on acidosis or glycosuria, but seemed to be more or less associated with hyperglycemia.

The urea index in six cases of fatal diabetic coma was abnormally low. Renal function appeared to become progressively worse as the

TABLE 9.—The Effect of Sodium Bicarbonate on the Alveolar Air, Plasma Chlorid and Chlorid Excretion, Case R. I. H., 2680 Calculated Sodium Chlorid in Plasma

Date	24 Hr. Urine Rate of Excretion	Sodium Chlorid Output Rate of Excretion in 24 Hrs.	Plasma Chlorid	Alveolar CO_2, Mm.	Remarks
10/16/15	2,000	3.40	6.01	20.1	
10/16/15	4,272	2.56	5.88	33.6	30 gm. sodium bicarbonate
10/17/15	2,000	0.80	5.85	28.7	
10/18/15	6,800	0.68	5.37	41.4	20 gm. sodium bicarbonate
10/19/15	2,200	1.32	5.58	30.1	
10/20/15	2,680	1.34	5.26	39.5	15 gm. sodium bicarbonate
10/21/15	5,000	Traces	5.23	44.1	10 gm. sodium bicarbonate
10/25/15	4,900	2.45	5.82	39.9	
			Case R. I. H., 2128		
3/20/16	5,690	14.20	5.93	23.2	
3/21/16	5,000	8.40	5.99	23.0	
3/21/16	3,000	2.22	5.35	38.6	20 gm. sodium bicarbonate
3/22/16	4,400	6.50	5.89	39.0	
3/24/16	3,635	4.82	5.97	33.2	

coma persisted. One patient had a pronounced accumulation of acetone in the blood plasma without a corresponding increase in excretion, and five patients showed a glycemia which seemed proportionally higher than the corresponding glycosuria. These cases suggest that fatal diabetic coma is accompanied by impaired renal function in which more than one of the kidney's functions are involved. The cause of the complication is not known.

In diabetes the blood plasma chlorid is usually lower than would be calculated from the chlorid excretion according to the formula of Ambard and Weill. This abnormality of excretion is not necessarily associated with acidosis, an abnormal urea index, the degree of glycemia or glycosuria.

Edema due to sodium chlorid retention may be encountered in diabetes. In one case it was accompanied by a falling urea index and by an increase of acetone in the blood without acidosis, as evidenced by an abnormally low alveolar carbon dioxid tension. The edema cleared up promptly when the sodium chlorid intake was restricted.

Edema following the administration of sodium bicarbonate is probably due to sodium chlorid retention, as the plasma chlorid diminishes and at the same time the excretion of sodium chlorid in the urine is lessened when the drug is given.

BOOK REVIEWS

PATHOGENIC MICRO-ORGANISMS. A Practical Manual for Students, Physicians, and Health Officers. By William Hallock Park, M.D., and Anna Wessels Williams, M.D., assisted by Charles Krumweide, Jr., M.D. Sixth Edition. Lea and Febiger, 1917.

The present edition of this well-known textbook conforms, as might be anticipated, in every way to the type of its respected predecessors. Indeed, it seems superfluous to review, and presumptuous to criticize, a book which has become so universally popular. Although written along the general lines of many textbooks of bacteriology, and containing essentially the same material, the wide experience of the authors with the practical as well as the purely scientific side of the work places a stamp of authority on many aspects of the subject which is usually lacking in similar treatises.

It is apparent throughout that real criticism has been exercised in handling the material. Thus, in the sections on technic, staining, and culture mediums the methods of actual value are emphasized, and hand in hand with the presentation of the theoretical side of immunity reactions are given excellent summaries of the technic and actual results of the various practical applications of these principles to diagnosis and treatment. Complement fixation in syphilis and other diseases, anaphylaxis and serum sickness, the opsonic index, ferments and antiferments, and leukocytic extracts are examples of the questions discussed. The sections on vaccine and serum therapy assume a rather liberal point of view, but one could hardly be more conservative without courting controversy. The remarks on diphtheria antitoxin are particularly concise and authoritative.

The sections on the systematic discussion of the various pathogenic microorganisms are clear and succinct, and the results of recent studies have been incorporated. Thus the division of pneumococci into groups by biologic reactions, the question of the virulence of diphtheria bacilli in relation to carriers, and the use of the Schick test may be mentioned among the many topics treated. One is interested to note the inclusion of the bacillus of Plotz as the cause of typhus fever.

The outlines of the bacteriologic examination of milk, water and foods, and the section on disinfectants include the methods which have been found valuable by the authors in connection with the work of the New York Health Board. The Carrel-Dakin method of disinfecting wounds is presented here probably for the first time in a general text.

The references, finally, should be invaluable to the student as leads for looking up the various subjects.